NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Metreleptin for treating lipodystrophy [ID861]

Evaluation Report

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Metreleptin for treating lipodystrophy [ID861]

Contents:

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Metreleptin for treating lipodystrophy [ID861]

This slide set is the pre-meeting briefing for this evaluation. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first evaluation committee meeting and should be read with the full supporting documents for this evaluation

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

History of the topic

- Following the company submission and ERG report development, the company advised of a change to its anticipated marketing authorisation
- Original anticipated population:
  - patients with congenital or acquired generalised lipodystrophy (GL), in adults and children 6 years of age and above;
  - patients with familial or acquired partial lipodystrophy (PL), characterised by leptin level < 12 ng/ml with triglycerides > 500 mmol/l and/or HbA1c > 8 %, in adults and children 12 years of age and above uncontrolled on standard therapy
- Updated population:
  - with confirmed congenital or acquired GL, in adults and children 2 years of age and above
  - with specialist-confirmed familial PL or acquired partial lipodystrophy, in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control
- Therefore, there are addendums available with results relating to the updated marketing authorisation
  - The clinical results and considerations in the main company submission and ERG report remain relevant to the updated population, however the results from the economic analyses are superseded by the results presented in the addendums

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Key issues for consideration

Clinical evidence

- Does the committee consider that data for the comparator has been sufficiently identified?
- The trials include surrogate endpoints. Does the committee consider these endpoints to be reasonable and sufficiently predictive of long term effects?
- Clinical or 'patient-perceived' outcomes, such as organ damage or hyperphagia, are important components in the economic model. What is the committee's view on the clinical evidence available for these outcomes?
- No comparative data was available and treatment effect is based on changes from baseline in single arm metreleptin studies. What is the committee's view of the relative effectiveness of metreleptin? Does this vary across the generalised lipodystrophy and partial lipodystrophy populations?
- Is the evidence base generalisable to clinical practice in the UK?

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Key issues for consideration

Cost-effectiveness evidence

- The health state of a patient within the model is determined by a set of attributes. Does the committee consider that these attributes are comprehensive and appropriately incorporated?
- A matching exercise was conducted to incorporate data from the NIH follow-up study (for metreleptin) and the GL/PL natural history study (for the comparator) – the ERG has significant concerns about the methods used. Does the committee consider that the company's approach is sufficiently robust?
- Has mortality been appropriately captured?
- Company used discrete choice experiment (DCE) to estimate utility values. What is the committee's view on the methodology, and the validity of results presented?
- What is a reasonable disutility associated with hyperphagia?
- Does the committee consider it appropriate to consider results based on the availability of 3 vial sizes – the 2 additional vial sizes are expected to launch within the 1st 3 months of marketing authorisation?
- What are the most plausible ICERs and QALY gains?
- Population contains children: any additional considerations required?

Disease background

Lipodystrophy (LD)

- Lipodystrophy is a rare, heterogeneous group of syndromes characterised by the complete or partial loss or absence of subcutaneous adipose tissue
- Without sufficient adipose tissue the hormone leptin can become deficient
  - the body's system for regulating energy use and storage is disrupted
    - resulting in lipid accumulation in abnormal sites, such as the liver and muscle
- Often accompanied by severe neuro-endocrine and metabolic abnormalities including insulin resistance with resultant hyperinsulinemia and diabetes mellitus, hepatic steatosis or steatohepatitis, dyslipidemia and severe hypertriglyceridemia
- Patients can also experience progressive organ abnormalities in multiple organs, including the liver, kidneys, pancreas, and heart
  - which lead to increased morbidity and mortality, as well as impaired quality of life
- Additional significant consequences of lipodystrophy that impact on patient quality of life and well being include hyperphagia, female reproductive disfunction
- It is estimated there are approximately 200 people with lipodystrophy in England → a proportion will be eligible for treatment with metreleptin

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Clinical forms of lipodystrophy

- Lipodystrophy is generally classified on the basis of the extent or pattern of fat loss (generalised or partial) and whether the disease is genetic or acquired
- Generalised (GL), that is affecting the entire body:
  - congenital (inherited) generalised lipodystrophy
  - acquired generalised lipodystrophy

  The severity and burden of lipodystrophy is consistently high among patients with generalised lipodystrophy
- Partial (PL):
  - familial partial (inherited) lipodystrophy (extremely rare)
  - acquired partial lipodystrophy

  Presentation of partial lipodystrophy is more heterogeneous, with some patients exhibiting more severe metabolic complications
- Despite progress in identifying the molecular basis of many lipodystrophy syndromes, it is often diagnosed late in the course of the disease, or remains undiagnosed

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Company submission page 33 – 35

GL is associated with neuro-endocrine and metabolic derangements resulting in a plethora of severe comorbidities. Soon after birth, patients with CGL (also known as Berardinelli-Seip syndrome) demonstrate insatiable hunger and accelerated linear growth rates, but reduced subcutaneous adipose tissue. AGL, also known as Lawrence syndrome, is more common in females (females:males, 3:1) and appears usually before adolescence (but may develop at any time in life) with progressive loss of fat affecting the whole body including palms and soles .

The various forms of FPL are extremely rare. Numerous genetic mutations have been identified for FPL including the LMNA gene in familial PL type 2 (FPLD2). The most prevalent form of FPL is FPLD2, also known as the Dunnigan-Variety. FPLD2 develops during puberty, resulting in gradual atrophy of subcutaneous fat in the extremities followed by fat loss in the anterior abdomen and chest, giving the appearance of increased muscularity. APL, also known as Barraquer-Simons syndrome, typically has a childhood or adolescent onset. APL is distinguishable from other LD syndromes by the unique cephalocaudal progression of subcutaneous fat loss that is observed

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Current treatment options

No standard clinical pathway

- There is no standard clinical pathway and no licensed treatments available
- The disease is currently managed with lifestyle modifications: such as a low fat diet and exercise; cosmetic surgery; and medications to manage the metabolic disturbance associated with leptin deficiency, including lipid lowering drugs (fibrates and statins) and medications for diabetes (metformin, insulin, sulphonylureas, and thiazolidinediones)
- Treatment with metreleptin is currently provided, as part of an early access programme (*EAP*), under the National Severe Insulin Resistance Service at Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust
  - [redacted] patients receiving metreleptin ([redacted]
- It is assumed that [redacted] new patients each year would be eligible for metreleptin treatment [redacted]

Metreleptin (Myalepta)

Aegerion

Anticipated indication wording	'Indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy patients: • with confirmed congenital or acquired generalised lipodystrophy, in adults and children 2 years of age and above • with specialist-confirmed familial partial lipodystrophy or acquired partial lipodystrophy, in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control'
Mechanism of action	Metreleptin is an analogue of the human hormone leptin, which is secreted into the circulation from adipocytes.
Admin & dose	The recommended daily dose of metreleptin is based on body weight, with a starting daily dose of: • Males and females ≤40 kg: 0.06 mg/kg (injection volume: 0.012 ml/kg) • Males >40 kg: 2.5 mg (0.5 ml), Females >40 kg: 5 mg (1 ml)
List price	List price: £2,335 per vial 11.3mg (10mg dose)* Simple discount patient access scheme (PAS) approved

***2.5mg and 5mg doses will be available within 3 months of metreleptin launch**

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Decision problem

	Final scope	Deviations
Population	People with generalised or partial lipodystrophy	As per marketing authorisation
Intervention	Metreleptin	-
Comparator	Established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes)	No data for comparators included in the clinical effectiveness analysis; ERG stated there were no systematic attempts to identify comparator studies and no selection criteria for reported
Outcomes	• Improvement in metabolic abnormalities • Liver function • Glucose control and diabetes satiety • Pancreatitis • Use of other drugs • Organ damage including heart and kidneys • Growth and development • Reproductive dysfunction • Infection • Mortality • Adverse effects of treatment • HRQL (for patients and carers; including effects on appearance)	No data provided on liver cirrhosis, complications of diabetes, organ damage or effects on appearance Mortality and pancreatitis only reported re. adverse effects of treatment Company also included ability to perform school or work; improvement in other metabolic abnormalities; direct mortality benefit of treatment, anxiety /depression; chronic pain, muscle spasms; family and caregivers ability to work

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The ERG highlighted that studies assessing the clinical effectiveness list only metabolic and adverse events outcome measures. All other outcomes data appear to be derived from publications of outcome data collected ad hoc by study investigators.

Comparators: Company FAC response: No data for the comparator were included in the clinical effectiveness section of the CS, however they were provided in the cost-effectiveness section and in response to clarification questions (not a factual error)

Interviews with LD patients conducted at the NIH in the US on behalf of Aegerion (1/2)

- Leptin deficiency observed in patients with LD may result in a significant reduction in the ability to regulate hunger and energy metabolism
- Hyperphagia, characterised by the ever-present pursuit of food, is an overwhelming burden for patients
- Patients are highly constrained by food access issues, impacting on many aspects of their daily lives including attending school, work and social situations
- Patients also suffer from mood and sleeping problems
- The extreme level of food seeking additionally creates stress on families/carers
- Carers may need to provide 24/7 supervision, especially as patients may also consume inappropriate or non-food items
- Hyperphagia can lead to disruptive activity in young children, which can be socially isolating for their carers

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Interviews with patients with LD conducted at the NIH in the US on behalf of Aegerion demonstrates the negative impact of LD (company submission Section 7)

Interviews with LD patients conducted at the NIH in the US on behalf of Aegerion (2/2)

- Female patients with LD can suffer reproductive dysfunction
- Adverse impact including polycystic ovary syndrome (PCOS), infertility and miscarriage are well documented
  - Can lead to significant deterioration in quality of life and be highly stressful; negatively affects psychological well-being, interpersonal functioning and sexuality
- Following miscarriage, women can experience post-traumatic stress, anxiety and depression
  - Experience of pregnancy loss and infertility can also have a considerable impact on partners
- Patients with LD can experience anxiety and depression due to the clinical burden of the disease including impaired physical appearance
- Other symptoms such as fatigue and frequent infection/illness, in addition to hyperphagia and anxiety/depression, can lead to impaired or complete inability to work or attend school, as well as to social isolation

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Interviews with patients with LD conducted at the NIH in the US on behalf of Aegerion demonstrates the negative impact of LD (company submission Section 7)

Patient expert comments

Patient experts (1/2)

- Day-to-day life can be very difficult → dealing with the constant hunger
  - '*I could eat a three-course meal and still be as hungry as if I hadn't eaten at all. I never felt satisfied*'
- Patients are highly constrained by food access issues, impacting on many aspects of their daily lives including attending school, work and social situations
- *'Self confidence in relationships are very much affected plus on-going fatigue and pain, which is largely unexplored by the medics*'
- '*…the comments about my appearance over the years have affected my confidence in my appearance to the point where I always cover up i.e. long sleeves, trousers only and no skirts/dresses or shorts*'
- Medical professionals sometimes overlook/misdiagnose the condition
  - '*Most patients in this community wait on average 7 years for a correct diagnosis, often with several misdiagnoses along the way*'
- There are worries about risk of suffering or passing the gene to family

Patient expert comments

Patient experts (2/2)

- Fatigue has a tremendous impact on the daily life
  - '*It makes it very difficult for me to do my job*'
- Expenses related to LD
- '*I also experience a lot of pain related to my increased muscle mass and because I cannot have help on the NHS, I've had to source a private physio for monthly sessions to ease the tension and make the pain bearable'*
- Metreleptin is the only treatment in LD → positive impact of treatment on metabolic profile, satiety levels, everyday life
  - '*Commencement of leptin treatment has made a big difference to my wellbeing*'
  - '*With earlier diagnosis and treatment with Leptin I would still be working and would have the quality of life I had before*.'
- Access to treatment might be limited for some people depending on their geographic location
  - '*Financial impacts are travel to Addenbrooke's and self-funding some injection equipment not available on prescription*'

Clinical expert and professional organisation comments (1/2)

- Metreleptin aims to improve metabolic status and reduce long term morbidity and premature mortality in patients with lipodystrophy
- It represents a single agent solution to many of the disease manifestations and there are no current similar alternatives to this solution
- Treatment is already available for patients with lipodystrophy attending the specialist service at Addenbrooke's Hospital
  - Patients have been treated for several years → there would be a negative impact on these patients if metreleptin therapy was no longer available
- Pathway followed at the Addenbrooke's Hospital is well defined for patients referred to the service
  - Some patients are seen in adult and paediatric Diabetes and Endocrinology centres elsewhere in the UK, where the pathway is variable depending on the centre
- The patients/carers need to be educated on how to administer leptin and then need 6-12 monthly follow up appointments

Clinical expert and professional organisation comments (2/2)

- Clinically meaningful endpoints difficult to demonstrate with metreleptin treatment in limited trial duration
  - Although surrogate endpoints demonstrated in trials (HbA1c, lipid levels, liver function tests) are reasonable
  - Reduction in HbA1c has been shown to predict an improvement in long term macrovascular and microvascular outcomes in patients with diabetes; reduction in fasting triglycerides will predict a reduction in episodes of pancreatitis
    - Improvements in these endpoints would be expected to predict clinically important long-term impacts on future health
- Long-term safety data is not generally available for metreleptin, although some patients have been taking this medication for up to 14 years or more
- Generalised lipodystrophy responds very well to metreleptin treatment, there is a variation in response in partial lipodystrophy

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NHSE comments

- Metreleptin is only initiated at one expert centre for a small number of patients who have generalised or partial lipodystrophy
- No investment is required to introduce the technology
- The Severe Insulin Resistance service has reported that metreleptin reliably abolishes acute pancreatitis in patients with partial lipodystrophy

Completed and ongoing clinical trials

Clinical effectiveness - Source

	Description	Aim of study
Clinical trials	NIH 991265/20010769* (pivotal, 1 patient from UK)	Integrated dataset to evaluate safety and efficacy of metreleptin in children and adults
	FHA101^ (supportive, expanded access study in the US)	Provide metreleptin under a treatment protocol to patients with LD associated with diabetes mellitus and/or hypertriglyceridaemia, and to evaluate the long-term safety and efficacy
	Pivotal evidence relevant to the decision problem	
Ongoing observational studies	NIH Follow-up study (Parameters for the metreleptin arm)	Evaluate disease status prior to metreleptin initiation and outcomes following therapy
	GL/PL Natural History study (Parameters for the standard of care arm)	Describe characteristics of patients, survival, and assess association of disease severity with survival; the extent to which patients experience burden associated with GL/PL
	Used in economic model	
	EAP *– results expected in Q1/Q2 2018 includes some UK patients, has been running for 10 years*	In the UK, treatment with metreleptin is currently provided, as part of an early access programme (EAP), under the National Severe Insulin Resistance Service at Addenbrooke's Hospital

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The results for the NIH follow-up study and the GL/PL natural history study, which were used to inform cost effectiveness modelling, were not included in the clinical effectiveness section of the company submission. The ERG has presented these results wherever possible.

Metreleptin is available in other parts of the world (e.g. countries in Europe) through an Early Access Programme (EAP), including in England. However, as part of the EAP, treatment with metreleptin in England is currently provided by a single centre at Addenbrooke's Hospital which is part of Cambridge University Hospitals (CUH) National Health Service (NHS) Foundation Trust, where there is a service specification (A03/S(HSS)/b) in place

Main clinical trial evidence

	NIH 991265/20010769	FHA101
Design	Pivotal, open-label, single arm	Open-label, single arm, expanded-access trial
Duration of study	Continuous enrolment over 14 years (2000-2014): NIH 991265: 8 months NIH 20010769: Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months	Continuous enrolment over 6 years (2008-2014): Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months
Population	Patients with GL (aged 1–68) or PL (aged 10–64)	Patients with GL* (aged 9–67) or PL (aged 23–67)
Population (n)	GL=66, PL=41 (1 patient from UK)	GL=9, PL=32
Key outcomes	Actual change from baseline in HbA1c at Month 12 Percent change from baseline in fasting serum triglycerides at Month 12	

HbA1c- Glycated haemoglobin; * associated with diabetes mellitus and/or hypertriglyceridaemia

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Additional information can be found in ERG report Section 4 and in company submission Section 4

Simha, et al. 2012 - met the pre-specified inclusion criteria but was excluded from the CS

Both studies report data for surrogate outcomes. The ERG stated that clinical or 'patient-perceived' outcomes, such as organ damage or hyperphagia, are more relevant than biochemical markers of 'surrogate outcome measures', such as triglyceride levels or HbA_{1c}. The ERG stated that improvements in these measures are not, in themselves, evidence of a treatment effects on long-term health outcomes.

The NIH follow up study additionally included outcomes such as hyperphagia, organ abnormalities, physical appearance, ability to perform work/school, mortality

Differences in baseline characteristics in main clinical trials

Higher proportion of GL patients in NIH study, in FHA study baseline metabolic measures are not as elevated as those in the NIH study

	NIH 991265/20010769		FHA101	
Characteristic	GL (N = 66)	PL (N = 41)	GL (N = 9)	PL (N = 32)
Acquired LD	21 (31.8)	6 (14.6)	6 (66.7)	3 (9.4)
Congenital/Familial LD	45 (68.2)	35 (85.4)	2 (22.2)	29 (90.6)
Fasting leptin, ng/ml, median (range)	1.0 (0.2, 5.3)	5.9 (1.0, 16.9)	NA	NA
HbA1c, % Median (range)	8.7 (4.5, 13.7)	7.8 (4.6, 13.3)	8.4 (5.1, 10.2)	8.0 (5.6, 12.8)
Fasting triglycerides, mmol/L Median (range)	14.5 (25.29)	12.0 (22.85)	3.3 (1.5, 120)	3.2 (0.7, 50.4)
ALT, >ULN, n (%)	49 (74.2)	14 (34.1)	5 (55.6)	23 (71.9)
AST, >ULN, n (%)	36 (54.5)	10 (24.4)	4 (44.4)	9 (28.1)

Premature discontinuation in **NIH study**: 23/66 (*34.8%*) of GL patients, 15/41 (*36.6%*) of PL patients; in **FHA study**: 4/9 (*44.4%*) of GL patients; 20/32 (*62.5%*) of PL patients

Key: NA – not available/applicable, ALT - Alanine aminotransferase, AST - Aspartate aminotransferase, ULN - Upper limit of normal 19

The NIH991265/ 20010769 study included a much higher proportion of participants with GL, 66/107 (62%) than the FH101 study, 9/41 (22%). In study NIH 991265/20010769 the median age of the GL group was 15 years with 68% of patients <18 years of age; patients in the PL subgroup were older (median age 38 years) than those in the GL group, with 84% ≥18 years of age. In study FHA101 most patients in both groups were ≥18 years of age at the time of enrolment. In general, the baseline metabolic measures for patients in study FHA101 were not as elevated as those for patients in study NIH 991265/20010769.

CS pages 87 and 88: The most common reason for discontinuation in the NIH study was patient noncompliance (5 GL patients, 8% and 6 PL subgroup patients, 19%), also people who had been transferred to other programs (8 in the GL population, 2 people in the PL population). In the FHA101 study, the most common reason for discontinuation was withdrawal by patient (1 patient (11.1%) in the GL population, 9 patient (28.1%) in the PL population).

Baseline characteristics in the GL/PL natural history study – used to inform standard of care arm in economic model

Participants had generally lower levels of HbA1c and triglycerides than participants in the main clinical trials

Characteristic	GL (N = 56)	PL (N = 122)	All* (N=178)
LD type, n (%)			
Acquired	5 (8.9)	26 (21.3)	31 (17.4)
Congenital/Familial	49 (87.5)	96 (78.7)	145 (81.5)
Fasting leptin mean (SD)	1.2 (0)	8.8 (7.7)	8.3(7.7)
HbA1c mean (SD)	8.1 (3.4)	7.4 (2.0)	7.5 (2.2)
Fasting plasma glucose mean (SD)	150.0 (116.6)	163.7 (71.5)	160.0 (84.6)
Fasting triglycerides mean (SD)	5.4 (3.7)	5.1 (6.9)	5.1 (6.3)
ALT, >ULN, n (%)	5 (31.3)	13 (26.5)	18 (27.7)
AST, >ULN, n (%)	3 (18.8)	5 (10.6)	8 (12.7)
Liver damage	15 (26.8)	27 (22.1)	42 (23.6)
Kidney damage	4 (7.1)	14 (11.5)	18 (10.1)
Heart damage	8 (14.3)	10 (8.2)	18 (10.1)
Pancreatitis	2 (3.6)	8 (6.6)	10 (5.6)

*50% of Turkish ethnicity, no patient from UK; **ERG comment**: study did not report any information about changes in markers of glycaemic control or lipid metabolism over time

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The CS does not include a description of the methods or baseline participant characteristics of the 'GL/PL natural history study', which was used to provide comparator data for the cost effectiveness modelling. A summary of the study protocol and baseline participant characteristics were provided in the company's response to clarification questions. ERG reproduced them (can be seen in ERG report Table 8 and 9)

Differences in baseline characteristics of the population in the clinical trials used to inform the economic model

NIH Follow-up study population, including the 107 participants in the NIH 991265/20010769 study

Characteristic	All patients N=112	GL patients N=68	PL patients N=44
Impaired physical appearance	86 (77%)	56 (82%)	30 (68%)
Disruption to female reproductive system	45 (80%)	21 (78%)	24 (83%)
Heart abnormality	50 (45%)	36 (53%)	14 (32%)
Hyperphagia	88 (79%)	57 (84%)	31 (70%)
Kidney abnormality	71 (63%)	46 (68%)	25 (57%)
Liver abnormality	105 (94%)	63 (93%)	42 (95%)
Pancreatitis	44 (39%)	21 (31%)	23 (52%)

- *Proportion of patients with liver, kidney or heart damage at baseline, or with a history of pancreatitis was generally higher than in the GL/PL study*

ERG comment: matching exercise (*relevant to the cost effectiveness model*) does not indicate that either ethnicity or baseline metabolic measures were considered when matching participants from the NIH Follow-up study to participants from the GL/PL natural history study

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The matching exercise outlined in section 17.6.2, Appendix 6, pages 270-271 of the CS, does not indicate that either ethnicity or baseline metabolic measures were considered when matching participants from the NIH follow-up study to participants from the GL/PL natural history study. Definitions of organ damage differed between the NIH follow-up study and the GL/PL natural history study, and the proportion of patients with liver, kidney or heart damage at baseline, or with a history of pancreatitis was generally lower in the GL/PL natural history study than in the NIH follow-up study. This may be because the metreleptin intervention study included patients who were at a later stage of LD than the GL/PL natural history study, where the baseline period is defined as the time before first GL/PL diagnosis

NIH 991265/20010769 study results

Statistically significant improvement *in reduction of HbA1c and triglyceride levels observed at 12 months (vs. baseline)*

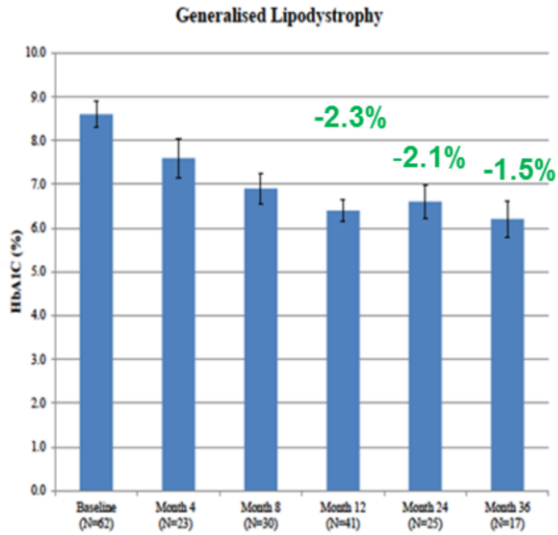
Change from baseline in HbA1c (%), full analysis set		
	GL N = 62	PL N = 39*
Baseline value (Mean, SD)	8.6 (2.33)	8.0 (2.18)
Month 12 value, LOCF (Mean, SD)	6.4 (1.68)	7.5 (1.84)
Effect size: actual change from baseline (Mean, SD)	***-2.2 (2.15)***	***-0.6 (1.22)***
95% Confidence Interval	-2.7, -1.6	-1.0, -0.2
Statistical test	P values computed using paired t-tests	
	<0.001	***0.005***
Change from baseline in triglycerides (mmol/L), full analysis set		
	GL N = 62	PL overall N = 39*
Baseline value (Mean, SD)	14.7 (25.66)	12.5 (23.35)
Month 12 value, LOCF (Mean, SD)	4.5 (6.10)	5.4 (7.37)
Effect size: percent change from baseline (Mean, SD)	***-32.1 (71.28)***	***-20.8 (47.93)***
95% Confidence Interval	-51.0, -13.2	-51.0, -13.2
Statistical test	P values computed using paired t-tests	
	0.001	***0.013***

*excluding results for a patient who had an outlier value – terminated from treatment Source: Table C22 Company submission 22

ERG comment: Simha et al. 2012, which assessed the effects of leptin therapy in 24 female patients with Dunnigan variety FPL and moderate or severe hypoleptinemia and found no significant change from baseline to six months in fasting glucose, insulin, glucose tolerance, or HbA1c levels (page 45 ERG report)

Persistence of metreleptin treatment effects

Least-squares mean change in HbA1c (%) at baseline and months 4, 8, 12, 24 and 36 in NIH 991265/20010769 study



- **Company**

From baseline to Month 36, statistically significant reductions measured by mixed model repeated measures (MMRM)

  - GL population: -1.4% ($p<0.001$)

Source: Figure C19 Company submission

ERG comment: Data for the overall PL population (not included in the CS) indicated persistence of the metreleptin effect on HbA1c over time

LS mean (SEM) percentage change values were as follows: month 12 = -1.2 (0.48), p = 0.014; month 24 = -1.9 (0.94), p = 0.044; month 36 = -2.0 (1.00), p = 0.049
Overall MMRM = -0.8 (0.26), p=0.002

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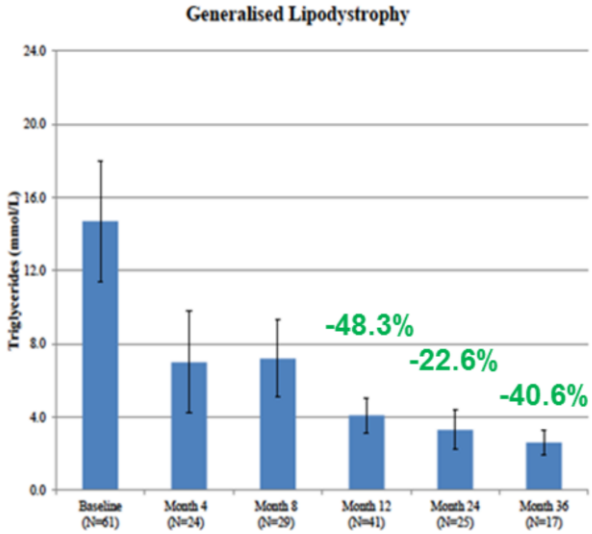
PL population, overall MMRM: At month 24 data were only available for 8 participants and at month 36 data were only available for 7 participants

Additional data were presented in the CS (pages 96-97) to support the persistence of these effects to 36 months.

Persistence of metreleptin treatment effects

Least-squares mean change in triglycerides (mmol/L; excluding outlier patient) at baseline and months 4, 8, 12, 24 and 36 in NIH 991265/20010769 study



Company

- **From baseline to Month 36, statistically significant** reductions measured by MMRM
  - GL population: -22.4% ($p<0.001$)

Source: Figure C19 Company submission

ERG comment: Data for the PL population (not included in the submission) indicated no statistically significant change in triglyceride levels over time

LS mean (SEM) percentage change values were as follows: month 12 = -16.7 (8.62), p = 0.054; month 24 = -9.4 (16.41), p = 0.566; month 36 =4.4 (17.53), p = 0.801; Overall MMRM = -8.3 (5.46), p=0.131

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Additional data were presented in the CS (pages 96-97) to support the persistence of these effects to 36 months

Subgroup analysis: Glycaemic control and lipid metabolism results from NIH 991265/20010769 study

Greater mean decreases from baseline to Month 12 amongst patients who had ***higher baseline percentage HbA1c and triglyceride levels***

	GL population	
	HbA_{1c}	Triglycerides
	Mean (SD) actual Δ to Month 12	Mean (SD) percent Δ to Month 12
Baseline HbA_{1c} (%):		
<6.5	-0.1 (0.35)	-4.1 (55.58)
≥6.5	-2.8 (2.08)	-41.2 (73.97)
≥7	-2.8 (2.08)	-41.2 (73.97)
≥8	**-3.0 (2.13)**	-38.6 (78.36)
Baseline triglycerides (mmol/L):		
<2.26	-1.6 (1.71)	6.7 (44.20)
≥2.26	-2.3 (2.28)	-42.5 (73.87)
≥5.65	**-3.3 (2.56)**	**-72.0 (25.09)**
LD type		
Congenital/ Familial	-1.8 (1.92)	-22.2 (80.54)
Acquired	**-2.9 (2.47)**	**-53.5 (39.09)**

Abbreviations: Δ, change; GL, generalised lipodystrophy; HbA_{1c}, glycated haemoglobin; PL, partial lipodystrophy; SD, standard deviation; US,

Source: Table C23 Company submission

No equivalent analyses are available for the PL population

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Company submission: Analyses for the evaluation of efficacy were conducted on pre-specified patient subgroups based on a number of factors, including baseline metabolic abnormalities, age, LD subtype, and region. A summary of the key findings from the subgroup analyses are shown in Table C23

Clinical results of FHA101 study

Improvement in reduction of HbA1c and triglyceride levels observed at 12 months (vs. baseline)

Change from baseline in HbA1c (%)		
	GL	**PL**
	N = 9	N = 29
Baseline value (Mean, SD)	7.7 (1.99)	8.1 (1.77)
Month 12 value, LOCF (Mean, SD)	6.2 (1.96)	7.8 (1.76)
Effect size: actual change from baseline (Mean, SD)	-1.2 (2.53)	-0.4 (1.49)
95% Confidence Interval	-4.3, 2.0	-1.0, 0.2
Statistical test	P values computed using paired t-tests	
	0.360	**0.210**
Change from baseline in triglycerides (mmol/L)		
	GL	PL overall
	N = 9	N = 29
Baseline value (Mean, SD)	19.9 (40.90)	8.5 (12.37)
Month 12 value, LOCF (Mean, SD)	7.6 (11.10)	6.4 (10.06)
Effect size: percent change from baseline (Mean, SD)	-26.9 (78.32)	8.7 (93.39)
95% Confidence Interval	-124.1, 70.4	-29.1, 46.4
Statistical test	P values computed using paired t-tests	
	0.486	**0.640**

Source: Table C24 Company submission

ERG comment: reported decreases ***were not statistically significant***

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The smaller, single arm metreleptin treatment study, FH101, reported decreases in percentage HbA1c and triglyceride levels, from baseline to month 12 of treatment, in all patient groups. However, these decreases were not statistically significant. Full results for markers of glycaemic control and lipid metabolism are provided in Table 14 (ERG report), reproduced from the CS (CS, Table C24, pages 103-105).

Clinical results
Other relevant outcomes (1/3)

Effect of metreleptin on hepatic enzymes

- NIH 991265 - changes in ALT and AST, from baseline to month 12 of treatment
  - For the GL population the mean changes were -53.1 and -23.8 respectively
  - For the PL population the mean changes were -0.4 and -5.1 respectively
- ERG comment: ***median*** (range) ***values show a wide range → are not clearly supportive of a treatment effect***
  - The median (range) change in AST from baseline to 12 months of treatment was -331.0 to 734.0 for GL patients, and -65.0 to 54.0 for all PL patients
- *Effect of metreleptin on hyperphagia*
- NIH 991265/20010769: metreleptin treatment of 14 patients (12 with GL and 2 with PL) dramatically decreased food intake at 4 months from 3,170 kcal/day to 1,739 kcal/day
- ERG comment: study also reported mean food intake at 12 months (n=6) and these data indicated a subsequent increase in food intake to 2,015 (410) kcal/day → ***not significantly different from baseline***

Key: ALT: Alanine aminotransferase AST: Aspartate aminotransferase

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Additional information can be found in ERG report: page 80 - 92

Clinical results
Other relevant outcomes (2/3)

Effect of metreleptin on liver volume

- NIH 991265: Liver volume of 21 patients with GL and 8 patients with PL assessed at baseline → 20 and 6 patients had hepatomegaly (liver volume >2000 mL), respectively
  - Reductions in liver volume observed in 15 (71%) of the 21 patients with GL and an additional 4 patients had reductions on or after Month 12
    - Reductions in liver volume for these 19 patients ranged from 7% to 71%, with most patients (12 of 19) having reductions of ≥30%
  - Among 8 patients in the PL population, 4 (50%) patients had reductions and an additional patient had reductions at all assessments on or after Month 12.
    - Reductions in liver volume for these 5 patients ranged from 8% to 51%
- ERG comment: The ***median (range) of observed change in liver volume*** (mL) from baseline to month 12 of treatment was ***-34.8*** (-53.9 to -10.0) ***for GL patients*** (n=12), and ***-16.7*** (-21.2 to 4.4) ***for PL patients*** (n=8)

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Additional information can be found in ERG report: page 80 - 92

Clinical results

Other relevant outcomes (3/3)

Effect of metreleptin on concomitant medication use

- NIH 991265/20010769 - 16 (41%) of 39 patients with GL on insulin at baseline discontinued use after starting metreleptin; 7 (22%) of 32 patients on oral antidiabetic medications at baseline discontinued use of these drugs; among 34 patients who received lipid-lowering therapies at baseline, 8 (24%) discontinued these medications
- ERG comment: the CS also states that: 'Many of these patients could discontinue the use of these therapies within the first 12 months of metreleptin treatment' - ***no times to discontinuation are reported***
  - No results from NIH Follow-up study reported, which shows that 41/64 (64.1%) of GL and 15/44 (34.1%) of PL patients discontinued antidiabetic medications. Most discontinuations were for bolus insulin or metformin, ***only 2 GL patients discontinued basal insulin or insulin + metformin***

Effect of metreleptin on growth and development

- Among 7 GL patients in the NIH 991265/20010769 study, 4 patients had delayed puberty prior to metreleptin and 3 had precocious puberty; after follow-up 2 patients had normal development on metreleptin and 1 patient continued to have delayed puberty

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Additional information can be found in ERG report: page 80 – 92

Effect on growth and development: Among the 14 patients without baseline data reported who were not prepubertal (normal for age), 13 patients reported normal pubertal onset and/or progression on metreleptin at a post-baseline assessment and 1 patient had delayed onset reported

Clinical results
Additional ERG comments (1/2)

- The clinical effectiveness section of the company submission ***did not report results of the effects of metreleptin treatment on reproductive dysfunction; pancreatitis; development or progression of heart or kidney damage; measures of health-related quality of life; mortality***

The ERG commented on the above outcomes and provided limited results, based on the available evidence

- **Reproductive dysfunction**;
  - ERG comment: NIH follow-up study: 21/27 (78%) of relevant female GL patients and 24/29 (83%) of relevant female PL patients experiencing reproductive dysfunction at baseline → 12 and 8 patients, respectively experienced improvements (no definition for improvement provided)
- **Pancreatitis** - pancreatitis is only reported as an adverse event occurring subsequent to metreleptin withdrawal
  - ERG comment: NIH follow-up study: 95% of effected GL patients and all effected PL patients experienced improvements in pancreatitis on metreleptin treatment ←→GL/PL natural history study: over the whole observation period 7/56 of GL patients and 20/122 of PL patients experienced at least one episode of pancreatitis
  - 5/7 (71.4%) effected GL patients and 12/20 (60.0%) of effected PL patients experienced pancreatitis during the follow-up period

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Additional information can be found in ERG report: page 80 - 92

Clinical results
Additional ERG comments (2/2)

- **Development or progression of heart or kidney damage**

  NIH follow-up study: 11/36 (31%) of GL patients and 1/14 (7%) of PL patients were classified as having experienced an improvement in their heart abnormality over 1 year of metreleptin treatment

  - ERG comment: 1 year changes in blood pressure alone are unlikely to provide an adequate indicator of long term clinical improvement
  - Of 32 GL patients who had no evidence of heart abnormalities before metreleptin treatment, 9 (28%) had emergent heart abnormalities after metreleptin initiation (6/30 (20%) of PL patients)

- **Measures of health-related quality of life including effects on appearance and activities of daily living**

- ERG comment: NIH follow-up study: at baseline, 56/68 (82%) of GL patients and 30/44 (68%) of PL patients were classified as having impaired physical appearance
  - 38 (68%) of the 56 effected GL patients and 14 (47%) of the 30 effected PL patients were reported as having post-metreleptin improvement
  - Patients experienced improvements in their ability to perform work or school work with metreleptin

- **Mortality** - No survival data are presented in the clinical effectiveness section of the CS
  - In cost effectiveness analyses data taken from GL/PL natural history and NIH Follow-up study

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- ERG reproduced the mortality tables from both studies

Additional information can be found in ERG report: page 80 – 92

- Improvement in heart abnormality (criteria): normal (systolic <120 and diastolic <100) at one year and had no additional emergent heart conditions during that year

- Measures of health-related quality of life including effects on appearance and activities of daily living: no definition of the criteria used to determine improvement was provided

- Mortality tables can be found in ERG report: Tables 17 and 18

Adverse events

- **NIH 991265/20010769 study**
  - In the GL population approximately 89% of people experienced a treatment-emergent adverse events (TEAE); 44% experienced severe TEAE and 8% of patients discontinued treatment due to a TEAE
  - In the PL overall population approximately 85% of people experienced a TEAE; 39% experienced severe TEAE and 2% of patients discontinued treatment due to a TEAE
  - The most common TEAEs were weight loss, hypoglycaemia, fatigue abdominal pain, nausea, hypoglycaemia, fatigue, alopecia and constipation
- **FHA101 study**
  - In the GL population approximately 78% experienced a TEAE; 67% experienced severe TEAE and 11% of patients discontinued treatment due to a TEAE
  - In the PL population approximately 84% experienced a TEAE; 28% experienced severe TEAE and 9% of patients discontinued treatment due to a TEAE
  - The most common TEAEs were hypoglycaemia, upper respiratory tract infection, urinary tract infection, nausea, anxiety, and sinusitis
- 4 deaths were reported in the NIH study and 2 deaths were reported in the FHA study
- 6 patients experienced (4 patients with GL and 2 patients with PL) treatment emergent pancreatitis across studies (1 patient died, 5 recovered)
- Injection site reactions were reported in 3.5% of patients across studies with metreleptin
  - All events have been mild or moderate in severity, none led to treatment discontinuation

ERG comment: the safety over lifetime treatment is unknown

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Further information can be found in CS: Section 9.7 and ERG report: Section 4.2.4

Page 111 CS: In general, when considering the difference in sample size, the types and incidence for commonly reported TEAEs in study FHA101 were similar to those reported in the pivotal study NIH 991265/20010769. Among the 9 patients with GL in Study FHA101, the most commonly reported TEAEs, all reported in 2 patients (22%), were hypoglycaemia, upper respiratory tract infection, abdominal pain, increased liver function tests, and ear infection.(10) For the 7 patients in the PL subgroup, the most commonly reported TEAEs were hypoglycaemia, upper respiratory tract infection, and urinary tract infection (each 3 patients, 43%), and nausea, anxiety, and sinusitis (each 2 patients, 29%). The only drug-related TEAE reported in more than 1 GL patient was hypoglycaemia (2 patients, 22%). In the PL subgroup, the only drug-related TEAEs reported in more than 1 patient were hypoglycaemia and nausea (each 2 patients, 29%)

Page 113 CS: Section 9.7.2.4 - data were pooled across studies and LD type in order to provide an overall summary of all adverse drug reactions reported in patients with GL (n=75) and patients in the PL subgroup (n=38) who were treated in the two LD studies NIH 991265/20010769 and FHA101. The only events reported in >10% of these 113 patients were weight decreased (15%) and hypoglycaemia (13%); fatigue was reported in 7% of patients and injection site reaction, neutralising antibodies, decreased appetite,

nausea, and alopecia were each reported in 4% of patients with all other adverse drug reactions reported in 1 (<1%) or 2 (2%) of the 113 patients.

Page 116 CS: Three cases of T cell lymphoma have been reported while taking metreleptin in clinical studies. All three patients had acquired GL. Two of these patients were diagnosed with peripheral T cell lymphoma while receiving the medicinal product. A separate case of anaplastic large cell lymphoma was reported in a paediatric patient receiving the medicinal product who did not have haematological abnormalities before treatment

Page 92 ERG report: CS concludes that the known side effects of metreleptin can be managed as part of the normal clinical practice for patients with this complex condition. The ERG notes that the CS does not report the safety concerns as highlighted in the Centre for Drug Evaluation and Research Report (not included in the CS) nor the associated risk evaluation management strategy (REMS). The summary of safety in this report states: 'The principal safety concerns with metreleptin are T-cell lymphoma and anti-metreleptin antibodies with neutralizing activity. These concerns are of sufficient magnitude to require REMS. Other safety findings that warrant inclusion in the Warning and Precautions section of the metreleptin labelling include hypoglycemia, autoimmunity, and hypersensitivity.'

ERG comments summary (1/2)

Issue	Critique
Search strategy	• Did not include any search term for comparators, only studies for the intervention retrieved, natural history studies may have also been missed
Excluded studies	• Appropriate studies excluded from search (e.g. Simha et al, study with female patients with PL)
Generalisability	• Very limited patient numbers from the UK (NIH study: 1 patient, FHA study: none; EAP: some patients – results expected in Q1/Q2 2018)
Evidence	• Lack of any comparative studies • Estimates of treatment effects are based on changes from baseline in single arm metreleptin treatment studies • No attempt to draw indirect comparisons through studies of the effects of established clinical management • Natural history study, used to provide comparator data for the cost effectiveness analysis, is not discussed in the clinical effectiveness analysis and has a population which is not comparable to metreleptin intervention studies

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Simha, et al. 2012 - met the pre-specified inclusion criteria but was excluded from the CS

ERG comment: Simha et al. 2012,50 which assessed the effects of leptin therapy in 24 female patients with Dunnigan variety FPL and moderate or severe hypoleptinemia and found no significant change from baseline to six months in fasting glucose, insulin, glucose tolerance, or HbA1c levels (page 45 ERG report)

ERG comments summary (2/2)

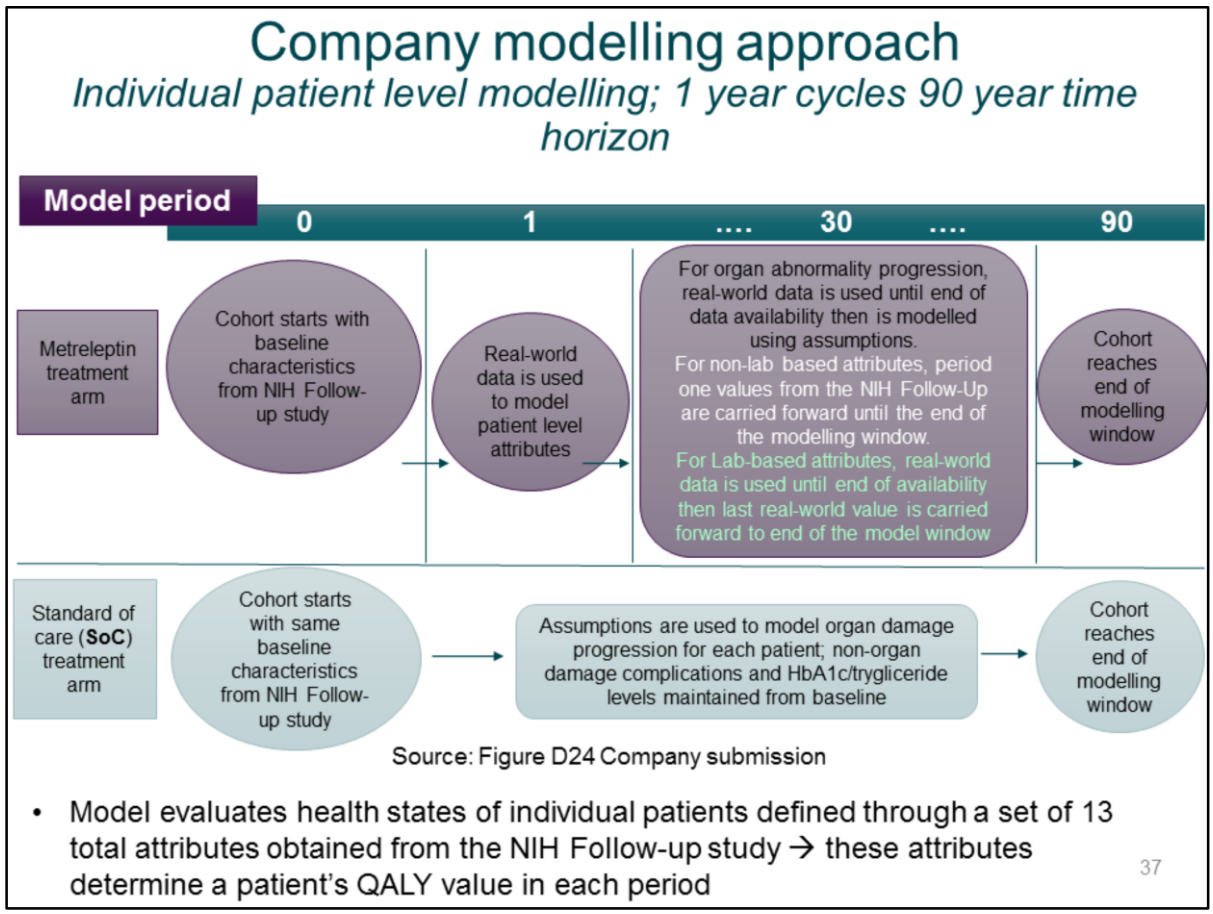
Issue	Critique
Evidence	• Clinical effectiveness analysis focuses primarily on changes in surrogate outcome measures (e.g. HbA1c, triglycerides, hepatic enzymes) • Very little information about any effects of treatment on patient-perceived symptoms and clinical outcomes (e.g. hyperphagia, organ damage → plays crucial part in cost-effectiveness model) • No data are provided on liver cirrhosis, complications of diabetes, organ damage or effects on appearance • Mortality and pancreatitis are only reported where these are considered to be adverse effects of treatment or, in the case of pancreatitis, discontinuation of treatment • Further data available from a Follow-up study (NIH Follow-up), which was used in cost effectiveness modelling, but was not reported in the clinical effectiveness analysis. 'Post-metreleptin improvements' reported in the Follow-up study are frequently based on measures taken at one year and use definitions based on changes in surrogate outcome measures

Cost-effectiveness section

Key issues for consideration

Cost-effectiveness evidence

- The health state of a patient within the model is determined by a set of attributes. Does the committee consider that these attributes are comprehensive and appropriately incorporated?
- A matching exercise was conducted to incorporate data from the NIH follow-up study (for metreleptin) and the GL/PL natural history study (for the comparator) – the ERG has significant concerns about the methods used. Does the committee consider that the company's approach is sufficiently robust?
- Has mortality been appropriately captured?
- Company used discrete choice experiment (DCE) to estimate utility values. What is the committee's view on the methodology, and the validity of results presented?
- What is a reasonable disutility associated with hyperphagia?
- Does the committee consider it appropriate to consider results based on the availability of 3 vial sizes – the 2 additional vial sizes are expected to launch within the 1st 3 months of marketing authorisation?
- What are the most plausible ICERs and QALY gains?
- Population contains children: any additional considerations required?



Individual patient health states can vary across periods when additional attributes are impaired, or when impaired attributes resolve due to treatment

Two identical cohorts with same baseline attributes populated at period 0, obtained from the baseline health states of all patients in the NIH Follow-Up study

New label indication is different from the label indication used in the original company submission and model
- From the NIH Follow-up study, 109 out of 112 patients would be eligible for the new indication (it was 80 out of 112 for the previously anticipated label indication) □109 patients populated the updated economic model
- 90-year time horizon (previously 60 years) based on ERG comments

The health state of a patient is determined by the set of attributes listed below, which indicates the level of impairment due to the disease.
- Organ impairment related attributes
  - Heart, kidney, pancreas and liver abnormalities (list of conditions that would fall under an organ abnormality is given in Figure 34 of the CS)
- Lab related attributes
  - HbA_{1c} levels (partial/ no response), triglyceride (partial/ no response) levels

- Other attributes
  Hyperphagia, ability to work/ perform at school, physical appearance, fast disease progression

In addition to the attributes above, hypoglycaemia events for each patient throughout his/her lifetime are also simulated in the model. The baseline values for these attributes at the start of the model are derived from the NIH follow-up study for both treatment arms.

Subset of four attributes play a crucial role in how mortality is simulated – abnormalities in heart, liver, kidney and pancreas
Patients can have 0, 1, 2, 3, or 4 organs with abnormalities

Evidence sources and assumptions (1/2)

Parameter	Source of parameter values
Initial patient distribution	Baseline from the NIH Follow-up study, both for SoC and metreleptin; 112 patients of which 109 are included in the updated MA and model
Transition probabilities for the organ impairment	Metreleptin arm: real-world data from the NIH Follow-up study, then extrapolation by a Markov process SoC arm: from start of the time horizon, disease progression is extrapolated by a Markov process (based on a subset of the GL/PL Natural History study; subset selected based on a matching method to make the baseline characteristics of the two studies similar)
Transition probabilities for blood-lab attributes (HbA_{1c} and triglycerides)	Metreleptin arm: NIH Follow-up study, then last observed carried forward (LOCF) method is used to extrapolate the blood-lab attributes SoC arm: assumed to remain unchanged throughout time horizon
Transition probabilities for other attributes	Metreleptin arm: some improvement assumed based on patterns in the NIH Follow-up study SoC arm: assumed to remain unchanged from baseline values
Adverse events (hypoglycaemia)	Metreleptin arm: real-world data from NIH Follow-up, then mean imputation method is used to extrapolate the number of hypoglycaemia events per year until the end of the time horizon SoC arm: assumption that patients do not experience hypoglycaemia events

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In the extrapolation of the remaining attributes other than blood-lab and organ damage (i.e. hyperphagia, ability to work, reproduction, physical progression and fast progression)
Metreleptin arm: some improvement assumed based on patterns in the NIH Follow-up study
SoC arm: assumed to remain unchanged from baseline values

ERG comment on other attributes: page 140 – 143
Issue 1) In the economic model, for each patient, a maximum of two measurements were provided for the following attributes: hyperphagia, ability to work, reproduction, physical progression and fast progression. For each of these attributes, the values under the "0" column were used for the SoC arm patients and the values under the "1" column were used for metreleptin arm patients. It is stated, in the company submission, that the values under the "1" column indicate the improvement from the baseline, however, details on the size/definition of these improvements were not provided.
(See company's answer in Response to clarification letter, page 28) The ERG asked whether this was a programming error or a deliberate assumption. The company acknowledged that it was a deliberate assumption, stating that they expect that any impairment would be likely to be indicated in the patient's medical data. Thus, when there is no evidence of an attribute being present, it was typically assumed that it was

absent.
The company stated that the only exception would be hyperphagia, stating that this was unlikely to be documented unless physicians were prospectively asked to assess it, whether or not it was present.
The company corrected the electronic model in the new version submitted, together with its response to the clarification letter. In the corrected model, patients with no hyperphagia data in period 1 were considered to experience the average treatment effect of metreleptin for their relevant group (i.e. patients with hyperphagia at baseline who lack metreleptin treatment data at period 1, will be assumed to have a hyperphagia with a probability of 0.09 in period 1 and onwards, since 9% of patients in the real-world data who suffer from hyperphagia at baseline continued to have hyperphagia in period 1). □ The ERG deemed these imputation approaches as speculative, since they were not based on evidence, but rather on assumptions/expectations.

Please also see Company and ERG FAC response on other attributes

Evidence sources and assumptions (2/2)

Treatment discontinuation	*Metreleptin arm*: discontinuation rate – weighted overall average value of 2.047% from NIH Follow-up study applied
Mortality	Survival information for patients treated with metreleptin from the NIH Follow-Up Study to end of data availability Time-varying Cox proportional hazards model is used to estimate the relationship between organ abnormality and mortality. This relationship is then applied to the NIH Follow-Up survival data to generate survival curves for each level of organ abnormality Mortality data from the National life tables in England used for patients with PL from the end of the NIH Follow-Up study until the end of the model time horizon
Utility decrements for the lipodystrophy complications	Discrete choice experiment (DCE) used to provide estimate of health disutilities for the key lipodystrophy attributes An additive approach is followed while implementing the disease attribute disutilities simultaneously A perfectly healthy individual was assumed to have a utility of 1

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A starting utility value of 1 was chosen not as an accurate reflection of a hypothetical patients' true health state but rather was chosen to minimise the number of patients with negative utility values after decrements are applied.

ERG comments
Model

- It is not clear that the NIH Follow-up study trial population is representative of UK lipodystrophy patients (1 patient from UK)
- Patient level modelling approach is appropriate but some concerns
  - How the final list of attributes included in the model were selected
    - It is unclear whether any other relevant and important attributes for lipodystrophy patients was not included in the model
  - Extrapolation approach used in the model for disease attributes ignores all possible interdependencies between disease attributes
    - Disease attributes are modelled/extrapolated independently of each other
  - Model applied extrapolation from different time points in the metreleptin and SoC arms
    - Difference in the start times for the extrapolation in the model might lead to an underestimation of the uncertainty for the patients receiving metreleptin
- Appropriateness of the model: lack of definitions of attributes and improvements attributed to metreleptin (e.g. improvement in hyperphagia)

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CS (page 192): Model is based on patients from the US NIH, which represents a patient population that is different from the patients currently treated in the EAP in the UK. The US NIH patient data used in the model are more advanced patients than those currently treated in the EAP in England. Model sensitivities have illustrated that treatment in patients at less progressed stages of disease can provide greater QALY gains and high value and this is expected to be the case in England

Company label update response document: The cost effectiveness model has been updated so that the "label indication" base case includes only patients who meet the criteria. Specifically, 3 patients who were treated with metreleptin at NIH did not meet the age restriction anticipated on the label and have been excluded from the "label indication" results. The resulting "label indication" group includes 109 patients (compared to 80 patients in our prior submission).

Organ impairment progression

- Abnormalities in four organs (heart, kidney, liver and pancreas) are considered in the model
- Progression probabilities estimated by fitting parametric survival curves to each of the KM curves from the NIH Follow-up study (*see probabilities below*)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	5.4%	4	1
1 to 2	5.0%	13	5
2 to 3	8.3%	47	17
3 to 4	3.9%	48	7
NIH Follow-up study included 114 patients, but sufficient data after baseline is available for only for 112, only 109 patients considered in the updated model			

Source: Table 71 in the CS

- The same extrapolation approach (Markov process for the total number of abnormal organs) is followed for organ impairment progression under SoC
  - Estimated transition probabilities derived from a subset of the GL/PL natural history study data are applied to patients from baseline until the end of the time horizon

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CS Page 258: It is assumed that organ abnormality events occur continuously and independently across patients and hence are well modelled by an exponential distribution. As such, exponential curves to all the Kaplan-Meier curves above to estimate the associated exponential parameter. The exponential parameter is then log transformed into a per period transition probability

Estimating transition rates from the NIH Follow-Up study, for patients treated with metreleptin, follows the same approach. However, patients are only observed from their date of treatment (rather than from birth), truncating the data and potentially biasing estimates. The approach

described above to generate transition probabilities derived from data on treated patients for the natural history study data is repeated for the NIH data.

The company stated that the baseline characteristics of the GL/PL and NIH follow-up studies differ substantially, for example, patients on metreleptin treatment on average, were at a more advanced stage of disease at start of observation compared to untreated ones. Therefore, the company obtained organ impairment progression transition probabilities for the SoC arm from a matched subset obtained from the GL/PL natural history study

ERG comments on organ impairment progression

- In the extrapolation of organ impairment progression, only the cumulative number of organ impairments (out of 4 organs) was taken into account
  - Not clear why the type of affected organ and the severity of an organ abnormality were not taken into consideration
- Differences between the NIH Follow-up study and GL/PL natural history study in baseline characteristics (see clinical section) and inherent structural censoring
  - Patients were observed from their enrolment time and onwards in the NIH Follow-up trial, whereas in the GL/PL natural history study, the retrospective patient records were collected to the earliest possible time point
- Staggering method (i.e. assuming one day in between two or more organ impairments that were observed simultaneously) → inadequate
- Lack of clarity regarding the approach of the incorporation of the time to event data from the NIH Follow-up study and from the GL/PL natural history study
  - Not clear whether a death event was considered as a censor or an organ impairment event (categorisation of the death event has a considerable impact on the hazard ratios)
- A patient's simulated number of impaired organs under SoC was forced to be higher than that patient's simulated number of impaired organs under metreleptin in each cycle
- Justification of methods: patient characteristics have no impact on the transition probabilities; organ impairment process possesses the Markov memoryless property → *it is not driving the final results that affect decision making*

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See comments in ERG report: page 115 – 125

Markov memoryless property: The company interpreted the results as indicating that there is no strong evidence for a consistent, significant correlation between time spent in the former state and time to progression, for the matched control patients from the GL/PL natural history study. This test was not conducted for NIH follow-up study, since the patients in this study were not followed from their birth.
The ERG considers that there could be other available tests for the Markov memoryless property, however the ERG also considers that the memoryless assumption is not the assumption that is driving the final results that affect decision making

Discontinuation rate (2.047%) only reflects impact of discontinuation in organ impairment progression. Not including impact of discontinuation on attributes such as blood-lab values, hyperphagia, ability to work creates a bias in favour of metreleptin

No de novo statistical analyses provided, in order to try to resolve concerns about organ impairment progression

Matching exercise

- Transition probabilities from the GL/PL natural history study were not used in the model → de novo organ impairment progression transition probabilities for the SoC arm were used, conducted on a matched subset obtained from the GL/PL study
- Matching exercise created pairs of patients from both studies (for each treated patient from the NIH Follow-up study, an untreated patient at a particular age from the GL/PL natural history study) whose reference age matched the treated patient's age and whose level of organ abnormality was close to that from the matched treated patient
- **ERG comments**: Company used a matching method outlined in NICE TSD 17, but ERG disagrees with the company on the appropriateness of the approach
- Method wasn't properly implemented: e.g. in the matching algorithm used by the company, for each patient died/censored in the GL/PL natural history study, pseudo patients that died/censored patient were created
- Insufficient interpretation of the matching results
  - The size of the untreated matched dataset (N=47) is approximately one third of the treated patients' dataset (N=112); suggests that an untreated patient is matched to multiple treated patients from the NIH Follow-up study → clinical inputs used in analysis not trustworthy

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ERG report: page 135 – 139

The company stated that the matching method employed in the CS was in line with NICE TSD 17, as it resembled the "nearest neighbour matching method", which was, according to the company, one of the two recommended matching methods (together with the propensity score matching) in NICE TSD 17. In the nearest neighbour matching method, a multivariate measure of distance (typically the Mahalanobis distance) is minimised between the matched pairs. Since Mahalanobis distance was mentioned in the NICE TSD 17 as a typical example, the company, in its response to the clarification letter, provided results for an additional matching exercise, which minimises the distance between the treated and untreated cohorts based on the Mahalanobis distance. In the latest submitted electronic model, the company used the transition probabilities derived from the matched untreated population based on the Mahalanobis distance minimisation method.

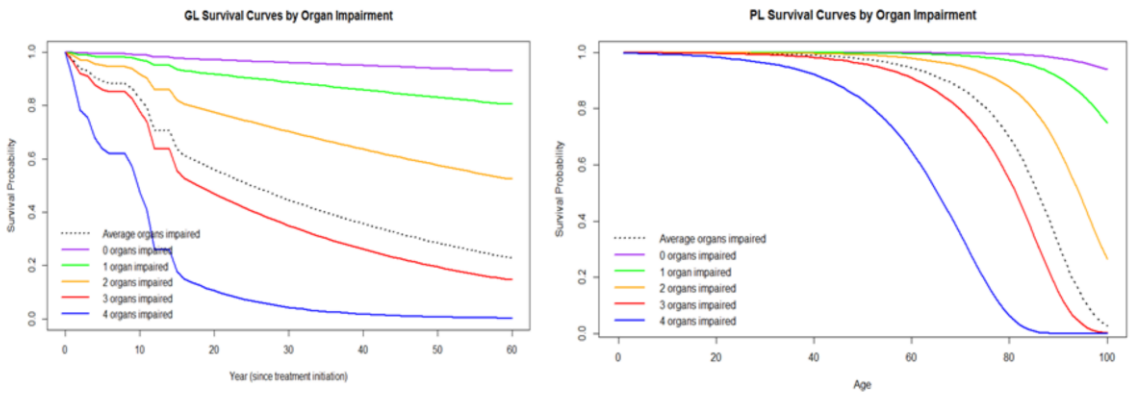
Derivation of mortality inputs for the model

Extrapolation of the survival

The hazard ratio from the Cox Proportional Hazards model is applied

- For GL patients, to the survival curve fitted to the patient level survival data from the GL sub-population of the NIH Follow-up study (*exponential distribution considered to be the best fit for extrapolation*)
- For PL patients, to the gender/age adjusted mortality figures from the UK life table (based on the sex ratio in the PL sub-population of the NIH Follow-up study)

It is assumed that survival is determined by the type of LD and number of organs impaired in a period (type, length of time have no impact)



Source: Company submission Figure 40 and 41

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Source: Figure 2 and 3 in company submission

The company stated that the Cox proportional hazards model yields a statistically significant (at 1%) coefficient on number of organs impaired, which remains significant in the presence of additional control variables, implying that the number of impaired organs has a significant (negative) effect on mortality.

The company also stated that PL patients from the GL/PL natural history study were not observed to experience mortality in excess of the general public (conditional on age and gender). Among PL patients in the NIH follow-up study, only one mortality was observed.

See figure 38 in the company submission for the KM vs. parametric curves

ERG comments

Mortality

- The ERG noted that the Cox PH model is fit on the natural history study data, to establish the relationship between organ abnormality and mortality. However, this hazard ratio is applied to parametric/life table survival curves obtained from the extrapolation of data from the NIH Follow-up study
  - For consistency, the same data sets should have been used
  - The company stated that the natural history study was used because of limitations in the NIH Follow-up study, but presented these results and also pooled results
- Lack of face validity for the GL/PL patient's survival extrapolation results (some GL/PL patients have a more favourable life expectancy than the general UK population)
  - The company agreed, and the updated model used the annual survival probability from the UK life table if the survival probability estimates based on the analyses on the NIH Follow-up and the GL/PL natural history studies were more favourable
  - ERG stated this is an artificial solution, instead reasons underlying the high survival outcomes from the model should have been explored
- ERG commented on the assumption that survival is affected only by the number of organs impaired
- Conditional survival curves derived based on a fixed number of organ impairments, whereas this is a time variant parameter
  - Therefore, baseline survival curves do not represent a patient population in whom number of organ impairments stayed fixed, and scaling these to conditional survival curves probably overestimated the difference in survival at later time points

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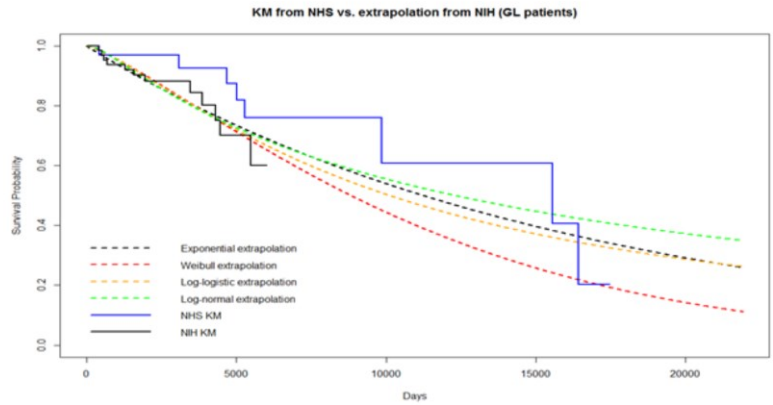
The company noted that, in the NIH follow-up study, information about the early stage of patients' disease was lacking and the observation window in the study was much shorter compared to the GL/PL natural history study.

ERG comments

Mortality

Clinical plausibility of the GL survival extrapolation

- The company presented results comparing the KM curve from the GL patients from the NIH Follow-up study with that from the GL/PL natural history trial after an age-based adjustment procedure had been applied (see figure below)



Source: ERG report, Figure 4

- The ERG stated that in this figure patients receiving SoC live longer
  - Additionally, it does not address why an exponential distribution is most appropriate

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The company, in its response to the clarification letter, presented the results from a validation exercise using survival data from the GL/PL natural history study. The validation exercise compared the KM curve from the GL patients from the NIH follow-up study with that from the GL/PL natural history trial after an age-based adjustment procedure had been applied. The resulting KM curves can be seen in Figure 4 above

Health-related quality of life

Utility decrements

- No EQ-5D data collected in trials → study Dhankhar et al. estimated the average EQ-5D score for lipodystrophy to be 0.67
  - EQ-5D domains not considered appropriate to capture attributes such as hyperphagia, female reproductive dysfunction, changes in physical appearance, or organ abnormality; additionally the study also included patients without LD
- Company conducted a discrete choice experiment (DCE) on a large sample of the general population → to estimate disutilities associated with key lipodystrophy attributes
- Baseline quality of life was derived from health states that patients inhabited at the beginning of the NIH trial
- For a given health state, a patient's quality of life was calculated by adding up the QALY decrements of those attributes present in that health state
- Baseline quality of life for patients with no attributes present was assumed to be 1 (perfect health)
- The company stated that the true decrement associated with hyperphagia is likely to be underestimated – explored in scenario analyses

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Respondents had to choose between two hypothetical health profiles that differed in levels of organ impairment, disease attributes and life expectancy

1,000 respondents surveyed : the US (250), UK (150), France (150), Germany (150), Italy (150) and Spain (150) → final sample matched Eurostat demographic characteristics for UK

Data obtained from the survey used to estimate a multinomial logit model → Three UK lipodystrophy clinical experts provided input for the survey and commented on the results

Utility decrements used in the cost effectiveness analyses

Attribute	Mean value	Standard error	Source
Heart Abnormality	-0.19	0.047	Company DCE and assumptions
Liver Abnormality	-0.15	0.038	
Pancreas Abnormality	-0.13	0.032	
Kidney Abnormality	-0.13	0.028	
Hyperphagia	-0.11	0.015	
Disruption to female reproductive function	-0.06	0.064	
Loss of ability to perform work / school	-0.25	0.047	
Impaired Physical Appearance	-0.10	0.025	
Triglycerides: Achieved Goal (<=200 mg/dL)	0.00	NA	
Triglycerides: Partial Response (>200 mg/dL, <=500 mg/dL)	-0.05	0.012	
Triglycerides: No Response (>500 mg/dL)	-0.11	0.028	
HbA_{1c}: Hypoglycemia	-0.01	0.004	
HbA_{1c}: Achieved Goal (>4.0, <=7.0)	0.00	NA	
HbA_{1c}: Partial Response (>7.0%, <=8.0%)	-0.08	0.02	
HbA1C: No Response > 8.0%	**-0.18**	**0.045**	

Table 33 ERG report

Table 33 shows the utility decrements used by the company in the economic model. Deterministic sensitivity analyses considered a 50% deviation from the mean value for the lower and upper limits. In the PSA, every utility decrement was assumed to follow a Beta distribution with the mean and standard error shown in Table 33.

ERG comments
HRQoL (1/2)

- Methodological issues in using DCE to directly obtain disutility values for health states
  - As long as these differences are not fully understood, the use of DCE disutilities to estimate QALYs *remains highly speculative*
  - For example, DCE classifies health states below zero more often than time trade-off and produces lower average health state values
    - Unclear why; anchoring, framing issues or choices being driven not only by differences by how easy it is to compare alternatives
- Concern around combining results from 6 countries whereas EQ-5D has country specific tariffs
- Long, complex survey with 12 attributes per card – cognitive burden
- Multinomial logit model: used to analyse the choice data
- These models have strong assumptions which have not been sufficiently tested
  - Age not included as an attribute whereas ERG considers age will impact weights of other attributes
- There are several attributes that the company mentioned as having impact on the patient's QoL, which were not included in the economic analyses due to lack of data (according to the company)
- E.g. pain, depression, retinopathy, neuropathy, amputation)

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Multinomial logit model (ERG report, page 153)

As the choices were always between two alternatives, this reduces to a logit model. These models have three strong assumptions: independence from irrelevant alternatives (or IIA) assumption, the identical and independent distribution (IID) assumption for the error terms and preference homogeneity. No information was provided in the CS or in the response to the clarification letter regarding any formal testing to check if these assumptions are satisfied. A mixed logit model which allows for preference heterogeneity should at the very least have been tested. It is quite possible that this alternative model would have had a substantial impact on the results. Thus, the model used by the company is most likely too simplistic for decision making.

ERG comments
HRQoL (2/2)

- The ERG highlighted concerns around the face validity of DCE based disutilities is low
  - In the metreleptin group 41.33 life years were accumulated*, translating into 16.27 QALYs, whereas for the SoC group 33.07 life years were accumulated, translating into only 0.27 QALYs
  - This implies that the average patient with lipodystrophy not receiving metreleptin values their health state as very close to death, which may be unlikely
- ERG agrees with company on limitations of EQ-5D values from Dhankar et al. (cross-sectional study; no information provided on clinical background of respondents; does not only include patients with LD, also could include carers)
  - However, given the issues with the utility scores obtained by the DCE study considers it to be an alternative
- Utility estimate from Dhankar et al. multiplied by life years gained obtained from the model presented in an ***exploratory scenario analyses by the ERG***

* Updated CE results, Table D46, undiscounted results

Resource use (1/2): Drug acquisition

Metreleptin acquisition cost

- List price: £2,335 per vial 11.3mg (10mg dose)
  - *Confidential simple discount PAS approved*
- Estimated annual cost per patient (list price): **£434,633.45**
  - *Assuming all three vials are available, and the proportion of patients receiving each vial size reflects the EAP data*

	11.3mg vial (10mg dose)	**5.8mg vial (5mg dose)**	**3mg vial (2.5mg dose)**
Proportion of EAP patients receiving each vial size	11.54% (n=3)	69.23% (n=18)	19.23% (n=5)
Abbreviations: mg, milligram; n, number			

  - *The company stated that the costs of home delivery and self-administration training will be funded by the company at no additional cost to patients or the NHS*

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Resource use (2/2): Cost of standard of care, hyperphagia and organ abnormalities

- Resource use was based on resource use questionnaires completed by two clinical advisers who treat lipodystrophy at Addenbrooke's Hospital
- Health-state costs were based on NHS reference costs
  - Costs associated with standard of care are estimated at £3,000 and were applied to patients in both treatment arms
  - Using the Health Resource Group (HRG) currency codes, the cost of abnormality of the heart is £11,888, £16,556 for kidney, £22,104 for liver, and £1,301 for pancreas abnormality
- In the model, *no costs for hyperphagia, PCOS, inability to perform school or work, impaired physical appearance, or abnormal laboratory levels were included*
- Only *adverse event cost of hypoglycaemia* was included in the model at a price of £1,087.07 per hypoglycaemia-hospital admission
  - **ERG comment**: Important adverse events (e.g. neutralising antibodies and treatment emergent acute pancreatitis) were overlooked – bias in favour of metreleptin
  - Impact expected to be **marginal**

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Base-cases considered in the economic analysis

- Base case 1 – metreleptin list price and a 10 mg vial size
- Base case 2 – metreleptin list price and all available vial sizes
- Base case 3 – metreleptin PAS price and a 10 mg vial size
- Base case 4 – metreleptin PAS price and all available vial sizes

Company's preferred base-case

Note: the PAS for metreleptin has been approved

Note: 10 mg vial size is currently being considered for marketing authorisation (MA) → vials of 2.5 mg, 5 mg and 10 mg will be approved within three months after MA; the PAS will apply to all vial sizes

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Cost effectiveness results

Company base case scenarios (discounted)

	LYs	QALYs	Costs BC1	Costs BC2	Costs BC3	Costs BC4
Metreleptin	19.18	8.34	£11,199,165	£5,749,294	[redacted]	[redacted]
SoC	16.23	0.58	£74,854	£74,854	£74,854	£74,854
Incremental	2.95	7.77	£11,124,311	£5,674,440	[redacted]	[redacted]
ICER	--	--	£1,432,391/ QALY	£730,654/ QALY	[redacted]/ QALY	[redacted]/ QALY

Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

Source: ERG addendum, Table 1

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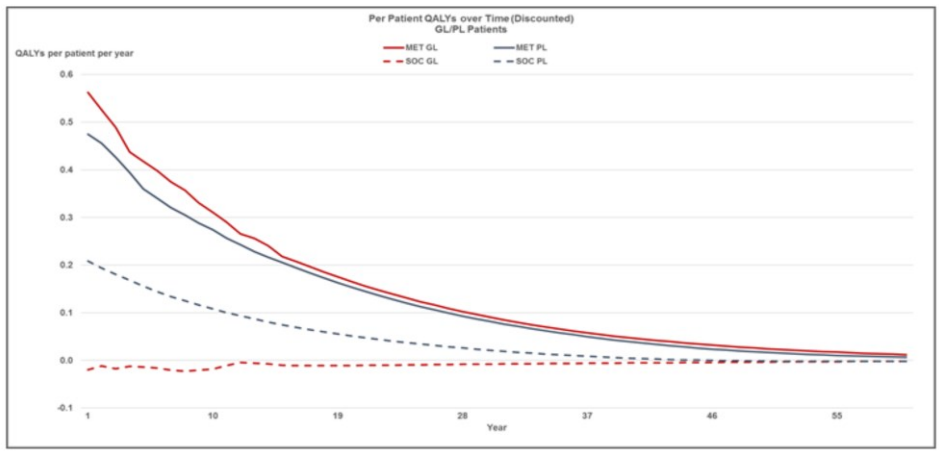
These results represent the updated base case scenarios after change in anticipated MA wording

QALY gains with metreleptin treatment

Distribution of QALYs per patient per year



Source: Figure 1 ERG addendum

- For GL patients in the SoC arm the number of QALYs per year are always negative or zero

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The distribution of the QALYs per patient per year for both treatment arms and partial lipodystrophy (PL) and general lipodystrophy (GL) patients separately is presented in Figure 1. In particular, this figure shows that for GL patients in the standard of care (SoC) arm the number of QALYs per year are always negative or zero.

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Sensitivity and scenario analyses (discounted)

Scenario	QALYs	BC1	BC2	BC3	BC4
Base case	7.77	£1,432,391	£730,654	[redacted]	[redacted]
*Double hyperphagia disutility + heart abnormality improvement**	*9.30*	*£1,206,039*	*£615,167*	[redacted]	[redacted]
Elimination of mortality benefit of metreleptin for PL	7.77	£1,438,784	£733,848	[redacted]	[redacted]
All organ progression probabilities increased by [redacted]	7.54	£1,461,201	£745,356	[redacted]	[redacted]
All organ progression probabilities decreased by [redacted]	8.05	£1,394,490	£711,266	[redacted]	[redacted]
Unadjusted natural history study organ abnormality progression probabilities used for SoC	8.02	£1,386,054	£707,002	[redacted]	[redacted]

*Company's preferred scenario

- **ERG comment**: Do not agree → there is no evidence that hyperphagia disutility should be twice as high from its DCE study estimate

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The ERG does not agree with that statement because there is no evidence that hyperphagia disutility should be twice as high from its DCE study estimate and also the argument that hypertension improvement is a surrogate for heart organ abnormality is deemed to be not convincing by the ERG.

Errors and changes in the updated model

- Company provided an updated model after change of the anticipated population
- ERG found ***additional changes*** in the updated model, other than updated label indication
  - These changes were not reported and led to differences in model results
    - the addendum model used slightly different proportional hazard regression coefficients compared to the original one
    - the hypoglycemic event that occurred in the 11th year of the 12th patient was deleted
    - irrelevant calculations in the organ impairment real world data sheets were mistakenly taken into consideration in the cells corresponding to the 63rd and 64th year calculations in the organ impairment simulation sheets
    - the missing baseline leptin levels are replaced with 9999, so that these patients will be always considered to fall under the updated license indication
- ERG **undid these changes in the addendum model, except for the last one**
- ERG identified ***two additional errors*** in the model: 1) Wrong transition probability is used for the fourth organ impairment annual probability for SoC 2) The costs and disutilities associated with organ impairments were wrongly calculated, and different formulae were used for SoC and metreleptin arms → ERG corrected them

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The ERG identified some programming errors in the model and some critical issues related to the input evidence used in populating the company's model. Please see ERG report Section 5

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ERG corrected company base case scenarios (discounted)

Marginal impact on results

	LYs	QALYs	Costs BC1	Costs BC2	Costs BC3	Costs BC4
Metreleptin	19.26	9.33	£11,202,756	£5,751,126	[redacted]	[redacted]
SoC	16.44	1.60	£72,635	£72,635	£72,635	£72,635
Incremental	2.82	7.73	£11,130,121	£5,678,491	[redacted]	[redacted]
ICER	--	--	£1,440,738/ QALY	£735,052/ QALY	[redacted]/ QALY	[redacted]/ QALY

Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

Source: Table 4 ERG addendum

ERG exploratory analyses

- ERG furthermore conducted ***six additional scenario analyses*** to explore structural and input parameter uncertainty:

1. Impact of *metreleptin discontinuation reflected not only in organ impairment progression, but in the progression of other disease attributes*. When patient on metreleptin discontinues the treatment, values from the SoC arm were assumed for discontinued patients' blood-lab and other attributes
2. Abandoning the constraint imposed on the SoC arm patients, which never allowed them to have *fewer number of organ impairments than metreleptin*
3. Assuming that there is *no difference between the SoC and metreleptin treatments in terms of the disease attributes other than organ impairment and blood-lab values* during a lifetime
4. Using *utility input from Dhankar et al.* (0.67) for all the years that a patient is alive
5. Except for the data at baseline, no *real-world data is directly used in the simulation of the organ/blood-lab attributes for the metreleptin arm* patients
6. For the disutility and cost calculations associated with the number of organs impaired, the *corrected formula from the metreleptin arm is used in both arms*

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ERG exploratory analyses results *(discounted)*

Scenario	QALYs metr.	QALYs SoC	QALYs gained	ICER BC1	ICER BC2	ICER BC3	ICER BC4
Base case	9.33	1.6	7.73	£1,440,738	£735,052	[redacted]	[redacted]
Scenario 1	7.29	1.60	5.69	£1,955,739	£997,801	[redacted]	[redacted]
Scenario 2	9.33	1.62	7.71	£1,443,359	£736,388	[redacted]	[redacted]
Scenario 3	3.56	1.60	1.96	£5,683,204	£2,899,521	[redacted]	[redacted]
Scenario 4	12.90	11.02	1.89	£5,898,649	£3,009,439	[redacted]	[redacted]
Scenario 5	7.26	1.63	5.64	£1,859,171	£948,041	[redacted]	[redacted]
Scenario 6	8.45	0.64	7.81	£1,425,279	£726,954	[redacted]	[redacted]

Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care

- Scenario 3 and 4 had the highest impact on the results – suggest that treatment effect of metreleptin on ***disease attributes other than organ impairment and blood-lab values*** and ***use of different utility values*** are key drivers

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The ERG stated that the model is not sufficiently validated and that the uncertainty around the ICERs goes beyond that parameter uncertainty. The ERG has been unable to identify an ERG preferred estimate because of the extent of uncertainties.

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime incr. QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr.)
Greater than or equal to 30	3

Undiscounted QALY gains

	QALYs Metreleptin	QALYs SoC	Incremental QALYs
Company preferred base case scenario	16.27	0.27	16
Company base case corrected by ERG	19.71	3.08	16.63
ERG's exploratory analysis 1	13.09	3.08	10.01
ERG's exploratory analysis 2	19.71	3.12	16.59
ERG's exploratory analysis 3	6.80	3.08	3.72
ERG's exploratory analysis 4	27.96	22.75	5.21
ERG's exploratory analysis 5	14.97	3.15	14.35
ERG's exploratory analysis 6	16.63	0.62	16.01

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Overall lipodystrophy (GL and PL) budget impact

Incorporating PAS price (BC4)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patient numbers	26	31	35	40	44
Uptake rate	85%	85%	90%	90%	90%
Number of patients treated	22	26	32	36	40
Other savings / costs*	£0	£0	£0	£0	£0
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Assuming availability of all three vial sizes of metreleptin (11.3mg vial, 5.8mg vial, and 3mg vial)
- The budget impact considers that: 11.54% patients receive the 10mg dose vial; 69.23% patients receive the 5mg dose vial; 19.23% patients receive the 2.5mg dose vial, as per the EAP December 2017 data
- ERG comment: high expected uptake rate reliable, but the reason behind the rising uptake is unclear
  - Discontinuation due to patient preferences/clinical recommendation was considered as 0% in the first 5 years, because of the small estimated patient numbers in the budget impact -- validity of assumptions remains unclear

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Equality

- No equality issues have been presented

Innovation

The company considers metreleptin is an innovative treatment because:

- only therapy specifically for LD, acting on the underlying cause of leptin deficiency → represents an important innovation in the management of LD
- availability of metreleptin in the UK will help foster investments in drug innovation for UK patients in currently underserved rare disease areas

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Metreleptin for treating lipodystrophy

Final scope

Remit

To evaluate the benefits and costs of metreleptin within its licensed indication for treating lipodystrophy for national commissioning by NHS England.

Background

Lipodystrophy is a rare, heterogeneous group of syndromes characterised by the complete or partial loss or absence of subcutaneous adipose tissue. Without sufficient adipose tissue the hormone leptin can become deficient and the body's system for regulating energy use and storage is disrupted, resulting in lipid accumulation in abnormal sites, such as the liver and muscle. Lipodystrophy is often accompanied by metabolic abnormalities including insulin resistance with resultant hyperinsulinemia and diabetes mellitus, hepatic steatosis or steatohepatitis, dyslipidemia and severe hypertriglyceridemia. It can therefore have a substantial effect on quality of life. Despite progress in identifying the molecular basis of many lipodystrophy syndromes, it is often diagnosed late in the course of the disease or remain undiagnosed.

Lipodystrophy is generally classified on the basis of the extent or pattern of fat loss (generalised or partial) and whether the disease is genetic or acquired. There are 4 major subtypes:

Generalised:

- congenital (inherited) generalised lipodystrophy
- acquired generalised lipodystrophy

Partial:

- familial partial (inherited) lipodystrophy
- acquired partial lipodystrophy

The prevalence of lipodystrophy varies from approximately 1 to 2 per 1,000,000 population depending on the subtype. Applying the prevalence estimates to the population of England for 2016[1] suggests there are approximately 200 people with lipodystrophy in England.

There are no licensed treatments in the UK for generalised or partial lipodystrophy. The disease is currently managed with lifestyle modifications: such as a low fat diet and exercise; cosmetic surgery; and medications to manage the metabolic disturbance associated with leptin deficiency, including lipid lowering drugs (fibrates and statins) and medications for diabetes

(metformin, insulin, sulphonylureas, and thiazolidinediones). A single National Specialist Service for people with lipodystrophy was established in 2011 at Addenbrooke's Hospital in Cambridge.

The technology

Metreleptin (Myalept, Aegerion Pharmaceuticals) is an analogue of the human hormone leptin, which is secreted into the circulation from adipocytes. Leptin acts centrally through multiple metabolic actions within the arcuate nucleus to affect body composition, appetite and metabolism. Metreleptin is administered by subcutaneous injection.

Metreleptin does not currently have a marketing authorisation in the UK for treating lipodystrophy. It has been studied in clinical trials in people with generalised or partial lipodystrophy.

Intervention(s)	Metreleptin
Population(s)	People with generalised or partial lipodystrophy
Comparators	Established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes)
Outcomes	The outcome measures to be considered include: • improvement in metabolic abnormalities • liver function (including cirrhosis) • glucose control and diabetes (including complications of diabetes and need for diabetes therapies) • satiety • pancreatitis • use of other drugs • organ damage including heart and kidneys • growth and development • reproductive dysfunction • infection • mortality • adverse effects of treatment • health-related quality of life (for patients and carers; including effects on appearance)
Nature of the	• disease morbidity and patient clinical disability

condition	with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical Effectiveness	• overall magnitude of health benefits to patients and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it • treatment continuation rules (if relevant)
Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.

Other considerations	• If the evidence allows, subgroups according to whether the lipodystrophy is generalised or partial, or congenital or acquired, and according to the presence of complications associated with lipodystrophy (including diabetes and hypertriglyceridemia) will be considered. • Guidance will only be issued in accordance with the marketing authorisation. • Guidance will take into account any Managed Access Arrangements
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England, Manual for prescribed specialised services 2016/17, Chapter 62: Highly specialist metabolic disorder services (adults and children), 2016 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf National Service Frameworks: Long Term Conditions (including neurological) – archived http://webarchive.nationalarchives.gov.uk/+/www.nhs.uk/NHSEngland/NSF/Pages/Longtermconditions.aspx Department of Health NHS outcomes framework 2016 to 2017 (2016) https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

[1] Population of England (2016) https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates Accessed October 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Metreleptin for treating generalised and partial lipodystrophy [ID861]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Aegerion Pharmaceuticals Limited (metreleptin) Patient/carer group • Black Health Agency • Children Living with Inherited Metabolic Diseases (CLIMB) • Contact a Family • Diabetes Research and Wellness Foundation • Diabetes UK • Genetic Alliance UK • Independent Diabetes Trust • Lipodystrophy UK • Muslim Council of Britain • National Children's Bureau • Network of Sikh Organisations • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Genetic Nurses & Counsellors • British Dietetic Association • British Inherited Metabolic Disease Group • British Society for Genetic Medicine • British Society for Human Genetics • British Society for Paediatric Endocrinology and Diabetes • Primary Care Diabetes Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of Paediatrics & Child Health	General • All Wales Therapeutics and Toxicology Centre • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Welsh Government • Welsh Health Specialised Services Committee Possible comparator companies • None Relevant research groups • Clinical Trials Research Unit • Cochrane Metabolic & Endocrine Disorders Group • MRC Clinical Trials Unit • National Institute for Health Research Associated Public Health Groups • Public Health England • Public Health Wales

Consultees	Commentators (no right to submit or appeal)
• Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Society for Endocrinology • Training Research and Education for Nurses in Diabetes (TREND UK) • UK Clinical Pharmacy Association • UK Genetic Testing Network • UK Health Forum <u>Others</u> • Department of Health • Great Ormond Street Hospital Metabolic Unit • Department of Endocrinology, University Hospital Birmingham Foundation Trust • NHS England • National Severe Insulin Resistance Service, Addenbrooke's Hospital • Oxford Centre for Diabetes, Endocrinology and Metabolism	

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Metreleptin for treating lipodystrophy

[ID861]

INTERIM

Specification for company submission of evidence

17 January 2018

Contents

List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	Antidrug antibodies
AE	Adverse event
AGL	Acquired generalised lipodystrophy
ALT	Alanine aminotransferase
APL	Acquired partial lipodystrophy
AST	Aspartate aminotransferase
BMI	Body mass index
BSCL	Berardinelli-Seip congenital lipodystrophy
CFAS	Controlled Concomitant Medication Full Analysis Set
CI	Confidence interval
CGL	Congenital generalised lipodystrophy
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical study report
CUH	Cambridge University Hospitals
EAP	Early Access Programme
EMA	European Medicines Agency
EMR	Electronic medical record
ESRD	End-stage renal disease
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FFA	Free fatty acid
FPL	Familial partial lipodystrophy
FPLD2	Familial partial lipodystrophy, Dunnigan variety/ familial partial lipodystrophy type
GI	Gastrointestinal
GL	Generalised lipodystrophy
GPRD	General Practice Research Database
HbA1c	Glycated haemoglobin
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IND	Investigational New Drug
LD	Lipodystrophy

LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
LS	Least squares
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measures
MPGN	Membranoproliferative glomerulonephritis
NIH	National Institutes of Health
NHS	National Health Service
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
PCOS	Polycystic ovary syndrome
PL	Partial lipodystrophy
PROMIS	Patient Reported Outcomes Measurement Information System
PSS	Personal social services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	System organ class
TEAE	Treatment-emergent adverse event
SOC	Standard of care
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
ULN	Upper limit of normal
US	United States

Executive Summary

Lipodystrophy is an ultra-rare disease with devastating consequences for patients and their caregivers characterised by the partial or complete absence of adipose tissue and impaired leptin production. The prevalence of this disease is estimated at ~1 per 1 million people, with a population well characterised in the United Kingdom at a single centre of excellence in Cambridge (Addenbrooke's - Cambridge University Hospital). Lipodystrophy patient survival is impaired as organ abnormalities progress. Overall survival reduction is estimated at ~25 years in generalised lipodystrophy (GL) patients. Partial lipodystrophy (PL) patients' organ abnormality progression is similar to that of GL patients once a first organ abnormality is present.

Lipodystrophy is a multi-factorial disease with numerous consequences stemming from the inability to store adipose tissue and from impaired leptin production (Section 6.1). Ectopic fat deposition occurs and patients experience progressive organ abnormalities in multiple organs, including the liver, kidneys, pancreas, and heart. Additional significant consequences of lipodystrophy that impact on patient quality of life and well being include:

- Hyperphagia (extreme hunger not satisfied by food intake at any level).
- Impact on the female reproductive system, with dysfunction including delayed puberty and infertility.
- Severe metabolic problems, including highly elevated triglycerides, severe insulin resistance (resulting in symptoms such as hirsutism and acanthosis nigricans) and poorly controlled blood glucose levels with early onset type 2 diabetes.

Lipodystrophy also has a profoundly detrimental impact on patient and family quality of life through numerous other symptoms including changes to physical appearance, work/school impairment, chronic pain) (Section 7.1). Most patients are affected from birth due to genetic/familial disease, with symptoms such as hyperphagia and organ abnormalities manifesting in childhood. Primary caregiver burden frequently includes limitations on ability to work, anxiety, and other factors affecting quality of life. Families are also greatly impacted (e.g., disproportionate amount of time and focus on the sick child, eating patterns affecting all family members and resulting tensions within families).

Metreleptin will be the first licensed treatment option for lipodystrophy patients (Section 8). Metreleptin replaces the leptin lipodystrophy patients fail to produce, directly addressing a critical patient need. Traditional treatment options generally target individual symptoms such as elevated HbA1c or triglycerides and patients are mostly refractory to these treatments (e.g., many patients are still uncontrolled with very high insulin doses). Metreleptin, by contrast, is successful in addressing metabolic symptoms resistant to traditional therapy (i.e., HbA1c, triglycerides) and dramatically improves many other facets of the disease unaddressed by traditional treatments, including hyperphagia, organ abnormalities such as pancreatitis, female reproductive dysfunction, ability to perform school or work, and other factors affecting quality of life. The organ abnormalities addressed by metreleptin are associated with early mortality and hence a reduction in mortality with metreleptin treatment can be achieved through reducing organ damage progression. Efficacy is seen even in very young patients, is sustained over time, and early intervention is warranted given the progressive nature of the disease without treatment. Caregivers and families also greatly

benefit: they may experience improved ability to work and the reduced psychological and physical burden of caregiving. The dramatic impact of metreleptin on the lives of patients and caregivers is supported by input from patients and caregivers and ongoing qualitative research.

The costs of lipodystrophy to the NHS/PSS prior to metreleptin are substantial, though data are limited due to the ultra-rare nature of this condition. Metreleptin is delivered by subcutaneous injection by the patient at home with initial training provided an independent nurse team that will be funded by Aegerion. Overall, introduction of metreleptin will create limited or no additional cost to NHS outside of the price of the drug while reducing the frequency of high-cost consequences of lipodystrophy and usage of alternative medications. Metreleptin is included within the specialised service specification of the National Severe Insulin Resistance service at Addenbrooke's and has been provided to patients under a manufacturer-sponsored early access programme (EAP) for up to 10 years. The centre of excellence at Addenbrooke's has developed leading expertise in delivering appropriate care for lipodystrophy patients. Further costs of lipodystrophy outside the centre of excellence are not well documented, despite the frequency of lipodystrophy-related hospitalisation and additional care required by these patients through their lifetime.

According to a lipodystrophy natural history study that has been conducted:

- About half of patients ultimately die in the hospital setting (typically through organ failure)
- A lower bound estimate is that about 20% of lipodystrophy patients will be hospitalised in a given year, with as many as 5 or more hospitalisations per year observed in some patients (Section 14.3)
- Due to the high efficacy of metreleptin, offsets to resource use and cost are expected:

    - 41% of patients with GL are able to discontinue high dose insulin after initiating metreleptin (Section 9.6.1.4.5) and 34% are able to discontinue all antidiabetic medications;
    - Curbing the progression of organ abnormalities such as pancreatitis is expected to reduce the costs associated with these abnormalities and their treatment (Section 12.3.7).

The clinical efficacy and safety of metreleptin has been evaluated in a pivotal, open-label, single arm study (NIH 991265/20010769: 107 patients with lipodystrophy treated with metreleptin for up to 14 years) and a supportive study (FHA101: open-label, expanded-access trial of 41 patients with lipodystrophy treated with metreleptin for up to 5.5 years) (Section 9.4). Metreleptin treatment was associated with clinically meaningful and statistically significant reductions in HbA1c and triglycerides that were sustained over long-term treatment in patients with GL and a subgroup of PL patients who have clinically similar metabolic disturbances as patients with GL (Section 9.6). Improvements in insulin resistance and hypertriglyceridaemia were substantial enough that some patients were able to discontinue use of insulin, oral antidiabetic medications and/or lipid-lowering therapies (Section 9.6.1.4.5). In addition, clinically meaningful improvements were observed in elevated hepatic enzymes and hepatomegaly, commonly used surrogate measures of hepatic steatosis (Section 9.6.1.4.3). Effects to improve hyperphagia were also described,

which is particularly important as improvement in hyperphagia due to relative leptin deficiency helps to break the cycle of excess food consumption that further exacerbates metabolic abnormalities as ingested fats are directed towards ectopic locations (Section 9.6.1.4.4; Section 7.2). Long-term follow-up data of metreleptin treatment in lipodystrophy patients over several years indicate an overall favourable safety profile (Section **Error! Reference source not found.**).

An economic analysis has been performed using an individual patient model to compare metreleptin with standard of care, adopting a lifetime horizon to capture short term health related quality of life benefits associated with reduced symptoms and consequences, and the long term quality of life and life years gained associated with slowing organ damage progression. The model uses metreleptin single arm trial data and LD natural history data to estimate treatment effect, and extrapolate benefits over the lifetime horizon. The patient population consists of patients with GL and PL, and in the current submission is in line with the currently expected licensed indication (which is still undergoing EMA review). Hence, current expectations are for the following patient populations to be covered by the license:

- patients with congenital or acquired GL, in adults and children 6 years of age and above;

- patients with familial or acquired PL, characterised by leptin level < 12 ng/ml with triglycerides > 500 mmol/l and/or HbA1c > 8 %, in adults and children 12 years of age and above uncontrolled on standard therapy.

Were this not to precisely represent the final license, Aegerion would update the economic analysis to reflect the patient population covered by the final marketing authorisation. The list price of metreleptin is £2,335 per 11.3mg vial (10mg dose), but as described below it is intended to introduce small vial sizes which will be linearly priced in line with the 10mg dose.

Based on the results of the economic analysis and broader considerations Metreleptin provides good value for money, generating high QALY gains and having a wider impact on patients' and caregivers' lives beyond that quantified or captured by the QALY estimates provided in this submission. The economic analysis presented in this submission uses a number of alternative base cases, associated with multiple vial sizes for metreleptin becoming available during the appraisal process, and the approval of the simple PAS that Aegerion has submitted to PASLU. At marketing authorisation only a metreleptin 11.3 mg vial will be available (delivering 10mg of drug), and at the current time the proposed PAS (a simple price discount of [redacted] on the list price) is still going through PASLU approval. Hence, an initial base case using the 10mg dose, and list price is presented (BC1), and the alternative base case for this vial size with proposed PAS price applied (BC2) is also presented (see separate PAS based economic analysis submission). However, within 3 months of metreleptin launch two further vial sizes will be requested as part of the marketing authorisation – providing 2.5mg and 5mg doses. As the starting dose of metreleptin is 2.5mg for men, 5mg for women and is weight based for patients below 40kg, the availability of these vial sizes will reduce drug cost and waste due to the price of these smaller vials being linearly priced per mg in line with the 10mg dose. Hence, two further alternative base cases are provided, based on the three vial sizes being available at list price, and with the PAS discounted price being applied to each vial size (BC3 and BC4, respectively). The estimated

incremental cost-effectiveness ratios (ICERs) with each of these alternative base cases are provided in the table below. Ultimately, within the time frame of this HST appraisal, BC4 is expected to become the only base case for decision making, as the three vials are fully expected to be approved, and assuming approval of the simple PAS submitted to PASLU. The ICER for BC4 is £342,908 per QALY gained with 8.11 QALYs gained estimated. The ICER associated with a further variation on BC4 includes changes to model assumptions to reflect utilities believed to be more reflective of patient experience than those in the base case but less well supported by currently available data (£300,329/QALY, and QALY gain close to 10 estimated – see BC4.1 in the table below).

Alternative base case ICERs for metreleptin vs. standard of care

	ICER	QALYs Gained	5 year cumulative budget impact
Base case, list price, single vial size (BC1)	£1,340,457	8.11	£133,045,965
Base case, list price, multiple vial sizes (BC2)	£684,009		£67,802,818
Base case, PAS price, single vial size (BC3)	£671,132		[redacted]
Base case, PAS price, multiple vial sizes (BC4)	£342,908		[redacted]
PAS price, multiple vial sizes, adjusted utility values (larger decrement for hyperphagia, allowance for improvement in heart abnormality) (BC4.1)	£300,329	9.37	Same as BC4
Key: BC, base case; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year			

The ICER associated with base case BC4 represents a cost-effective use of NHS resources for the treatment of indicated GL and PL patients due to a large QALY gain based on:

- The large improvement in quality of life and wellbeing through improvement of distressing and debilitating symptoms, particularly hyperphagia, reduced organ damage progression, and limitations on work and schooling;
- Improved survival linked to a reduction in organ damage progression.

However, it is likely that this does not fully quantify the direct QALY gains for patients, in particular as the utility values are based on a discrete choice experiment conducted in 1,000 members of the public (Section 10.1.9 and Appendix 17.5), and so may not fully reflect the patient experience and perspective. While this study shows concordance with existing literature on the utility value of symptoms such as diabetes, it is likely to have significantly underestimated the QoL impact of the unique symptoms experienced by lipodystrophy patients, notably hyperphagia (Section 10.1.9 and the utility technical appendix). This greater QoL impact is seen in feedback from actual patient interviews and testimonies (including continuing survey work in the UK designed to capture the patient experience of living with lipodystrophy and the benefits of metreleptin) (Section 7.1).

It is also likely that the survival benefit could be underestimated, due to the nature of the patient-level data currently available for metreleptin (and used in the model) as these patients were more severe and with more advanced disease prior to treatment than would be expected to be treated in the future in actual clinical practice in England and Wales (Section 12.2.1). Early intervention can lead to substantial QALY gains by preventing or slowing lipodystrophy's devastating progression, for example in particular in young children with congenital GL (Section 12.5.16). Value is expected to be especially strong among these patients due to a) the lower doses needed to treat these patients in youth, and b) high benefit of preventing the emergence of organ abnormalities and the progression of the disease in these patients. Finally, the incremental quantifiable QALYs in these patients with early treatment initiation result in QALY gained estimate of 12 or more 12.5.6.

A substantial level of unquantified health and non-health benefits are present, such as improvements in the QoL of carers/families of children and adults with lipodystrophy as well as benefits in improving school, study and work opportunities for the young/working age profile of most patients (Section 10.1.15). In addition, there has as yet been no quantification of the time spent in a caring role by family members, but this could be substantial based on patient/carer feedback. Combining these factors, we believe the QALY gain associated with health benefits for people affected, carers/family are likely to be well in excess of 10 QALYs, and would, if these additional factors were fully quantifiable, bring the ICER within the range NICE have stated in updated 2017 interim method guidance as representing an acceptable and cost-effective use of NHS resources . Overall, with also taking into account the wider non-health benefits, metreleptin can be considered a cost-effective use of NHS resources within the HST appraisal decision making framework.

Metreleptin is also likely to bring substantial service delivery improvements to the NHS within a specialised service, and offer renewed hope for patients without a current effective treatment option if it were not available. Metreleptin reimbursement would also ensure continued access to those already benefiting under the current NHS service specification. As a therapy used in some English patients for 10+ years through an early access programme (and up to 19 years in other countries), the target population and treatment is well understood. The benefits of metreleptin are large and have consistently been documented in international studies (e.g., US pivotal trial) and in England (e.g. UK EAP patients experienced similar HbA1c and TG benefits vs. the pivotal trial). In addition, the total budget impact of metreleptin treatment is anticipated to be moderate at [redacted] in the first year, with a cumulative five-year budget impact expected to be [redacted] (with PAS and the availability of multiple vial sizes). This is based on the current number of patients accrued over 10 years at Addenbrooke's (26) and the clinical experts' expectation of 6 new patients per year (2 GL, 4PL) being identified as requiring treatment (Section 13.1 and Section 13.7).

Aegerion is committed to support lipodystrophy patients and the NHS. Aegerion has invested heavily in the development, regulatory and commercial activities required to bring the product to the European market. The successful development of metreleptin, including a new, more patient friendly presentation is a key company focus. The evidence program to support this submission is unusually extensive for an ultra-rare disease program led by a small company, with a plethora of real-world outcomes studied and additional evidence development continuing:

- Creation of the largest dataset characterising the natural history of lipodystrophy when not treated with metreleptin:
- Multi-centre international study;
- First study to quantify impact of the disease on mortality and assess the patterns of organ abnormalities/disease progression and its link with survival impairment;
    - Comprehensive chart review effort with NIH experts to document the burden of lipodystrophy and the benefits of leptin replacement therapy beyond A1c and TG endpoints measured in pivotal trial;
- Characterisation of impact on hyperphagia, organ abnormalities, female reproductive dysfunction, schooling/work, etc;
- Discrete choice experiment conducted with ~1,000 participants across the US and 5 largest European countries to characterize impact on quality of life;
- Patient-level/transparent economic modelling (following guidelines).

The clinical evidence presented in this submission demonstrates the clinical efficacy and safety of metreleptin, and cost-effectiveness has been demonstrated versus standard of care. To ensure the cost-effectiveness, based on HST ICER criteria, and affordability of metreleptin, Aegerion will provide the therapy at a cost-effective price for the NHS and have proposed a PAS discount to achieve this.

In conclusion, lipodystrophy is a severe, life shortening condition where there is currently a high unmet need for an effective treatment such as metreleptin that can improve patient and carer/family quality of life, improve survival outcomes by slowing organ damage progression, and improve societal outcomes.

Section A – Decision problem

Section A describes the decision problem, the technology, ongoing studies, regulatory information and equality issues. A (draft) summary of product characteristics (SPC), a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR] should be provided.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1: Statement of the decision problem

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Population	People with generalised (GL) or partial lipodystrophy (PL)	• Patients with congenital or acquired GL • A subgroup of patients with familial or acquired PL, exhibiting more severe metabolic complications • Patients with familial or acquired PL	The original indication being sought from the EMA was as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency: • in patients with congenital or acquired GL, in adults and children 2 years of age and above • in patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA1c ≥6.5%, in adults and children 2 years of age and above uncontrolled on standard therapy Clinical efficacy and safety data from the clinical trials included a subgroup of PL patients related to the original indication, in addition to all eligible PL and GL patients. Of note, the definition of the PL subgroup and the age thresholds is currently under discussion in the regulator process and is likely to change prior to approval. The following indication is based on Day 180 questions: • in patients with congenital or acquired GL, in adults and children 6 years of age and above; • in patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
			and/or HbA1c ≥8%, in adults and children 12 years of age despite optimised standard treatment. The economic analysis includes the latest potential indication.
Intervention	Metreleptin	No variation	N/A
Comparator(s)	Established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes)	No variation	N/A
Outcomes	The outcome measures to be considered include: • improvement in metabolic abnormalities • liver function (including cirrhosis) • glucose control and diabetes (including complications of diabetes and need for diabetes therapies) • satiety • pancreatitis • use of other drugs • organ damage including heart and kidneys • growth and development	The outcome measures considered in the cost effectiveness assessment base case include: • improvement in metabolic abnormalities (e.g. triglycerides) • liver function (including cirrhosis) • glucose control and diabetes • satiety / hyperphagia • pancreatitis • organ damage to liver, heart and kidneys • reproductive dysfunction • mortality (linked to level of organ abnormalities)	Despite their prevalence, availability and potential impact of metreleptin, additional outcomes such as organ abnormalities, ability to perform work/schooling were not formally captured in the metreleptin clinical trials: To remedy this, Aegerion commissioned a large effort to collect the experience of lipodystrophy, both when untreated (Natural History) and when treated (NIH Follow up Study). The information gathered represents both a step-change in the understanding of the long-term consequences (e.g. in terms of organ abnormalities and mortality) of lack of adequate treatment for lipodystrophy patients, the breadth of the burden on lipodystrophy patients, and the benefits of metreleptin therapy in these patients. Some potentially important outcomes were not included in the cost effectiveness analyses due to insufficient data sources, and will be the focus of future research.

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
	• reproductive dysfunction • infection • mortality • adverse effects of treatment health-related quality of life (for patients and carers; including effects on appearance)	• adverse effects of treatment • Ability to perform school or work • health-related quality of life (for patients and carers; including effects on appearance) Other outcomes considered but not included in cost effectiveness assessment base case • improvement in other metabolic abnormalities (e.g. beyond triglycerides) • use / discontinuation of other drugs (including diabetes therapies such as insulin) • organ damage beyond liver, heart and kidneys • growth and development • infections • direct mortality benefit of treatment (e.g. beyond impact on organ abnormalities) • Anxiety/depression • Chronic pain and muscle spasms • Complications of diabetes including retinopathy,	Potential adverse effects of treatment such as hypoglycaemia, the development of neutralising antibodies, and lymphoma were considered and their impact on patient preferences were assessed. However, due to the lack of robust information on their (low) prevalence and the incremental role of metreleptin on their occurrence, their impact was not included in the base case cost effectiveness analyses.

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
		neuropathy, and amputation (e.g. toes, limb) • Impact on family and caregivers including ability to perform work • adverse effects of treatment Female infertility	
Subgroups to be considered	If the evidence allows, subgroups according to whether the lipodystrophy is generalised or partial, or congenital or acquired, and according to the presence of complications associated with lipodystrophy (including diabetes and hypertriglyceridemia) will be considered.	Subgroups included in the model were identified based on the labelled indication. The following subgroups were included in the economic analysis: GL; PL; CGL; all NIH patients including those who do not meet the label indication	N/A
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life Extent and nature of current treatment options	No variation	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements The nature and extent of the resources needed to enable the new technology to be used	No variation	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service Staffing and infrastructure requirements, including training and planning for expertise.	No variation	N/A

	Final scope issued by NICE	Variation from scope in the submission	Rationale for variation from scope
Special considerations, including issues related to equality	• Guidance will only be issued in accordance with the marketing authorisation. Guidance will take into account any Managed Access Arrangements	No variation	N/A
Abbreviations: EMA, European Medicines Agency; HbA1c, glycated haemoglobin; GL, generalised lipodystrophy; LD, lipodystrophy; N/A, non-applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PL, partial lipodystrophy; PSS, personal social services			

2 Description of technology under assessment

2.1 Give the brand name, approved name and when appropriate, therapeutic class.

Brand name:	Myalepta
Approved name:	Metreleptin
Therapeutic class:	Other alimentary tract and metabolism products, amino acids and derivatives, ATC code: A16AA07(1)

2.2 What is the principal mechanism of action of the technology?

Lipodystrophy (LD) is a rare, heterogeneous group of disorders characterised by partial or general absence of adipose tissue (fat cells).(2) Because of the loss of adipose tissue, levels of the adipocyte-secreted hormone leptin are very low.(3) Leptin is a naturally occurring, adipocyte-derived hormone and an important regulator of energy homoeostasis, fat and glucose metabolism, reproductive capacity, and other diverse physiological functions.(4, 5)

Metreleptin is a leptin replacement therapy administered to address the effects of leptin deficiency in the population of LD patients with low leptin levels. It is a recombinant human leptin analogue produced in Escherichia coli cells by recombinant DNA technology to form recombinant methionyl-human leptin.(1)

Metreleptin mimics the physiological effects of leptin by binding to and activating the human leptin receptor, which belongs to the Class I cytokine family of receptors that signals through the JAK/STAT transduction pathway.(1)

There are currently no structurally similar drugs. Metreleptin is the first treatment that targets the mechanism underlying the metabolic abnormalities of LD, namely leptin deficiency.

2.3 Please complete the table below

Table A2: Dosing Information of technology being evaluated

Pharmaceutical formulation	Powder for solution for injection (white lyophilised cake or powder).
Method of administration	Subcutaneous injection (self-administration)
Doses	The recommended daily dose of metreleptin is based on body weight, with a starting daily dose of: Males and females ≤40 kg: 0.06 mg/kg (injection volume: 0.012 ml/kg) Males >40 kg: 2.5 mg (0.5 ml) Females >40 kg: 5 mg (1 ml)

Dosing frequency	Once daily
Average length of a course of treatment	Not applicable; long-term chronic therapy given once daily
Anticipated average interval between courses of treatments	Not applicable; long-term chronic therapy given once daily
Anticipated number of repeat courses of treatments	Not applicable; long-term chronic therapy given once daily
Dose adjustments[a]	Based on clinical response (e.g. inadequate metabolic control) or other consideration (e.g. tolerability issues, excessive weight loss especially in paediatric patients), the dosage may be decreased, or increased to the maximum dosage of: Males and females ≤40 kg: 0.13 mg/kg (0.026 ml/kg) Males >40 kg: 10 mg (2 ml) Females >40 kg: 10 mg (2 ml)
[a] Language on adjustments may change in the final SmPC, based on D157 regulatory feedback received in November 2017	

Source: Draft Summary of Product Characteristics (SmPC) (1)

3 Regulatory information

3.1 Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

As an orphan drug, metreleptin is being reviewed under a full centralised procedure by the European Medicines Agency (EMA). A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) is expected in February 2018. The original sought after indication is as follows (1):

"Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency:

- in patients with congenital or acquired generalised lipodystrophy, in adults and children 2 years of age and above
- in patients with familial or acquired partial lipodystrophy, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA1c ≥6.5%, in adults and children 2 years of age and above uncontrolled on standard therapy."

While the severity and burden of LD is consistently high among patients with generalised LD (GL), the presentation of partial LD (PL) is more heterogeneous, with some patients exhibiting more severe metabolic complications. The indication being sought within PL includes the group of patients with more severe metabolic abnormalities regardless of standard treatment and lower leptin levels (referred to as

the PL subgroup hereafter). Clinical efficacy and safety data from the clinical trials included a subgroup of PL patients related to the original indication, in addition to all eligible PL and GL patients.

However, it should be noted that the precise characterisation of the PL subgroup and the age thresholds are currently under discussion in the regulatory process, The following potential indication is based on Day 180 questions:

- in patients with congenital or acquired GL, in adults and children 6 years of age and above
- in patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA1c ≥8%, in adults and children 12 years of age despite optimized standard treatment.

The final indication will not be known in time for the submission of the dossier but Aegerion will keep NICE updated. The economic analysis includes the latest potential indication.

3.2 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Metreleptin will be commercially available in England upon regulatory approval, anticipated to be May 2018.

3.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Metreleptin was approved by the Food and Drug Administration (FDA) in the United States (US) in 2014, where it is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired GL.(6) Metreleptin was also licensed in Japan in March 2013 for the treatment of LD (both GL and PL) to the pharmaceutical company Shionogi based on a study conducted by Shionogi.(7) It is available in other parts of the world (e.g. countries in Europe) through an Early Access Programme (EAP), including in England (see Section 3.4 and Section 8.1).

3.4 If the technology has been launched in the UK provide information on the use in England.

Metreleptin has not been launched in the UK. However, as part of the EAP, treatment with metreleptin in England is currently provided by a single centre at Addenbrooke's Hospital which is part of Cambridge University Hospitals (CUH) National Health Service (NHS) Foundation Trust, where there is a service specification (A03/S(HSS)/b) in place.(8) The service specification is for insulin resistant diabetes, which covers severe LD and includes the use of leptin replacement for severe LD and low leptin levels, but excludes the cost of the drug. (8) The service specification is for insulin resistant diabetes, which covers severe LD and includes the use of

leptin replacement for severe LD and low leptin levels, but excludes the cost of the drug. More details of the service specification are provided in Section 8.1.

4 Ongoing studies

4.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months

Table A3 presents the completed and ongoing studies of metreleptin in patients with LD.

The clinical development programme for metreleptin includes the following completed interventional clinical trials:

Study NIH 991265/20010769 (NCT00025883): Pivotal, open-label, single arm, clinical study to assess the efficacy and safety of metreleptin conducted at the US National Institutes of Health (NIH).

Study FHA101 (NCT00677313): An open-label, expanded-access trial with the primary objective to provide metreleptin under a treatment Investigational New Drug (IND) protocol to patients with LD, while establishing the long-term clinical effectiveness and safety as a secondary objective.

Data from the pivotal trial forms the basis of the EMA submission, with study FHA101 as supportive evidence. These trials were identified in the clinical systematic literature review (SLR) and form the basis of the clinical efficacy and safety of metreleptin.

In addition, there are ongoing observational studies involving patient experience with LD and treatment with metreleptin, including:

- A retrospective chart review study of 112 patients treated with metreleptin at the NIH, including patients enrolled in the pivotal clinical trial described above. The NIH Follow-Up study has allowed for consideration of longer history and follow-up across a range of outcomes not fully studied in the clinical trial. While the retrospective and observational nature of this single-arm study is acknowledged, a wealth of information about these patients' experiences with LD both before and after initiation with metreleptin has been reported, including outcomes such as hyperphagia, female reproductive dysfunction, damage to key organ systems, and death, as well as trial-reported outcomes such as leptin, triglyceride, and HbA1c levels. Data from this study has been used to inform the economic model;

- The metreleptin EAP is allowing for collection of data in a cohort of patients in Europe, with a total of 76 patients currently receiving treatment in 10 countries. For a subset of the enrolled patients, including 21 in the United Kingdom (UK) and 52 others in Spain, Italy, France, Germany, and the

Netherlands, some of whom initiated metreleptin over a decade ago, analysis of patient history and experience with metreleptin is being conducted. Data are being collected to match key clinical trial endpoints (e.g., triglycerides, HbA1c) and also covering a wide array of additional disease characteristics such as hyperphagia, female reproductive dysfunction, and damage to organ systems. The EAP is a single-arm observational study with recognised limitations associated with a lack of internal control but provides rich data on a significant fraction of LD patients in relevant countries, particularly the UK, over a period of multiple years. Data from an interim analysis is expected in Q1/Q2 2018;

- The GL/PL Natural History study is a retrospective, observational chart review study of LD patients from multiple sites in several countries (US, Turkey, Brazil). A total of over 175 patient histories have been evaluated to date, some with records covering >10 years. These patients have been treated with standard of care therapy and have not received metreleptin. The long duration of data availability as well as the large number of patients (in the context of an ultra-orphan disease) provides insight into the natural history of disease in LD. Data extracted from charts includes disease attributes such as levels of leptin, triglyceride, and HbA1c, appearance and progression of organ damage, female reproductive dysfunction, and death. Data from the natural history study has been used to describe the disease in Section B, and to inform the economic model.

Table A3: Completed and ongoing metreleptin studies

Study name	Intervention	Population	Objectives	Status	Primary study reference
NIH 991265/20010769 (integrated dataset) NCT00025883	Metreleptin	N=107 (GL=66; PL=41; PL subgroup[a] =31)	To evaluate the safety and efficacy of metreleptin in children and adults Primary endpoint: change from baseline in HbA1c and serum triglycerides at Month 12 Plasma glucose, liver volume, other lipid parameters, free fatty acids, and liver function tests were also evaluated as efficacy parameters	Completed	CSR(9)
FHA101 (Expanded Access Program in the US) NCT00677313	Metreleptin	N=41 (GL= 9; PL=32; PL subgroup[a] =7)	To provide metreleptin under a treatment protocol to patients with LD that is associated with diabetes mellitus and/or hypertriglyceridaemia, and to evaluate the long-term safety and efficacy of metreleptin Primary endpoint: change from baseline in HbA1c and serum triglycerides at Month 12 Plasma glucose and liver function tests were also evaluated as efficacy parameters	Completed	CSR(10)
NIH Follow-Up study (chart review)	Metreleptin	N=112 (including patients previously enrolled in the pivotal trial)	To evaluate disease status prior to metreleptin initiation and outcomes following metreleptin therapy including pivotal trial outcomes (leptin, HbA1c, triglycerides) and other LD-related conditions including hyperphagia and organ damage.	On-going	Data on file
Metreleptin EAP	Metreleptin	Currently, 76 patients with GL and PL are being treated with metreleptin as part of the EAP. The data being collected and analysed include a set of 73 patients in 6 EAP countries - UK, Italy, Spain (Phase I), France, Germany, Netherlands (Phase II).	To assess the impact of metreleptin therapy on GL and PL patients who are participating in or have participated in the EAP programme overall and for each country, using a retrospective analysis of EAP patient data collected anonymously from individual EAP sites. The study has three specific objectives: 1. Describe the burden of GL/PL prior to metreleptin initiation	On-going	-

Study name	Intervention	Population	Objectives	Status	Primary study reference
			2. Describe patterns of metreleptin use after initiating therapy 3. Describe the impact of metreleptin on patient health, such as organ damage and metabolic status measures such as HbA1c and triglyceride levels, associated with the severity of GL and PL		
GL/PL Natural History Study	Usual care	N=178 GL and PL patients treated at the NIH, the University of Michigan and Dokuz Eylul University (Turkey). All patients are metreleptin-naïve.	The study has three specific objectives: 1. To describe the demographic and clinical characteristics of patients with GL and PL 2. To describe the overall survival of patients with GL and PL and assess the association of disease severity markers (i.e., elevated glucose, triglycerides, low leptin levels) with survival 3. To describe the extent to which patients experience burden (e.g., organ damage and disease progression) associated with GL and PL and assess the impact of disease severity markers	On-going	Data on file
Abbreviations: CSR, clinical study report; EAP, Early Access Programme; HbA1c, glycated haemoglobin; GL, generalised lipodystrophy; LD, lipodystrophy; NIH, National Institute of Health; PL, partial lipodystrophy [A] PL subgroup, the original sought after indicated population for patients with PL i.e leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA1c ≥6.5%					

4.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

No other UK assessments are ongoing.

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No equality issues are anticipated for the appraisal of metreleptin.

5.2 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B – Nature of the condition

6 Disease morbidity

6.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.

6.1.1 Disease overview

LD syndromes are clinically heterogeneous inherited or acquired ultra-rare disorders characterised by selective but variable loss of adipose tissue, primarily subcutaneous fat.(2, 11) The disease is associated with severe neuro-endocrine and metabolic abnormalities which lead to increased morbidity and mortality, as well as impaired quality of life (QoL).(2, 5)

The loss of subcutaneous adipose tissue in patients with LD can range from partial to more generalised.(2) Due to the loss of subcutaneous adipose tissue, levels of the adipocyte-secreted hormone leptin are very low.(3) Leptin is a naturally occurring, adipocyte-derived hormone and an important regulator of diverse physiological functions such as energy homoeostasis, fat and glucose metabolism and reproductive capacity.(4, 5) The leptin deficiency observed in patients with LD may result in a significant reduction in the ability to regulate hunger and energy metabolism, as well as dysfunction in glucose and fat metabolism.(12)

LD syndromes are classified by aetiology, i.e., genetic or acquired, and by distribution of subcutaneous adipose tissue deficiency, i.e., generalised (occurring in a diffuse fashion) or partial (restricted to regional anatomical subcutaneous adipose depots), leading to 4 main categories: congenital generalised LD (CGL), acquired generalised LD (AGL), familial partial LD (FPL) and acquired partial LD (APL).(2)

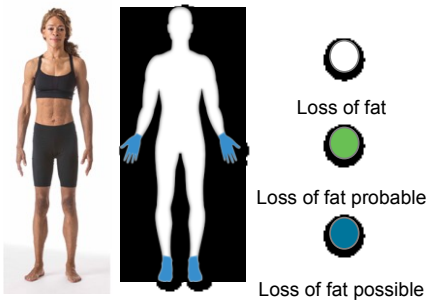
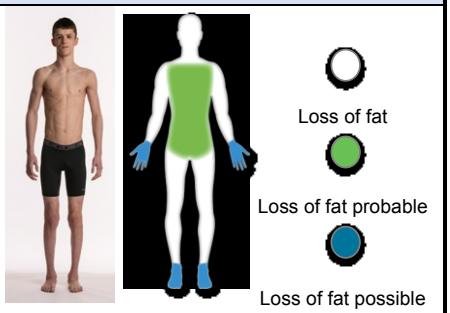
6.1.1.1 Generalised lipodystrophy

GL is associated with neuro-endocrine and metabolic derangements resulting in a plethora of severe comorbidities.(2) Soon after birth, patients with CGL (also known as Berardinelli-Seip syndrome) demonstrate insatiable hunger and accelerated linear growth rates, but reduced subcutaneous adipose tissue (Table B4).(13) Additionally, they may have prominent muscles, phlebomegaly, acanthosis nigricans, hepatomegaly and umbilical prominence.(2) The lack of subcutaneous adipose tissue leads to a leptin deficiency and a lack of energy storage capacity with consecutive ectopic fat accumulation in patients.(14) The leptin deficiency leads to an inability of the hypothalamus to regulate hyperphagia resulting in insatiable hunger and an increased food intake.(15) The fat deposition is associated with severe insulin resistance and hypertriglyceridemia which negatively impacts the function of the liver,

skeletal muscle, kidneys, heart and pancreas.(2) Multiple genetic causes have been identified, each with unique clinical features.(2)

AGL, also known as Lawrence syndrome, is more common in females (females:males, 3:1) and appears usually before adolescence (but may develop at any time in life) with progressive loss of fat affecting the whole body including palms and soles (Table B4).(16) AGL shares many features with CGL, including severely reduced subcutaneous adipose tissue and its associated complications.(13) Approximately 25% of AGL cases are associated with panniculitis, 25% with autoimmune disease, and 50% are of idiopathic origin.(17) Autoimmune disorders that have been associated with AGL include juvenile-onset dermatomyositis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome.(18)

Table B4: Essential features of GL

Type	CGL	AGL
Adipose tissue distribution		
Mean age of onset	0.3 years (range 0–12)	5 years (range 0–15)
Male:female ratio	1:1–2	1:3
Essential characteristics	Near complete lack of adipose tissue	Similar, but with progressive loss of fat (later age of onset) and no family history
Abbreviations: AGL, acquired generalised lipodystrophy (Lawrence syndrome); CGL, congenital generalised lipodystrophy (Berardinelli-Seip syndrome); GL, generalised lipodystrophy		

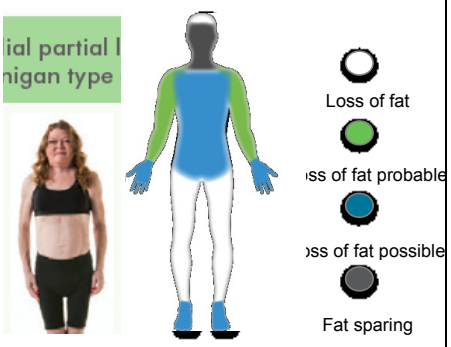
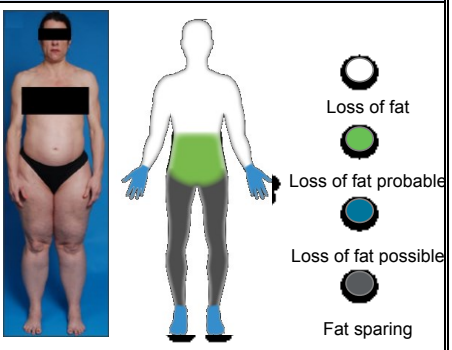
Source: Handelsman, 2013 (19); Brown, 2016 (2); Gupta, 2017 (16)

6.1.1.2 Partial lipodystrophy

Similarly, PL can be categorised as genetic/familial or acquired.(2) The various forms of FPL are extremely rare.(13) Numerous genetic mutations have been identified for FPL including the LMNA gene in familial PL type 2 (FPLD2).(20) The most prevalent form of FPL is FPLD2, also known as the Dunnigan-Variety.(13) FPLD2 develops during puberty, resulting in gradual atrophy of subcutaneous fat in the extremities followed by fat loss in the anterior abdomen and chest, giving the appearance of increased muscularity (Table B5).(13) Patients also have fat accumulation in the face, neck, and intraabdominal areas, causing a Cushingoid appearance.(21)

APL, also known as Barraquer-Simons syndrome, typically has a childhood or adolescent onset (Table B5). APL is distinguishable from other LD syndromes by the unique cephalocaudal progression of subcutaneous fat loss that is observed.(13) Subcutaneous adipose tissue loss begins in the face and subsequently spreads to the neck, upper extremities, thorax and abdomen.(13) The lower extremities, lower abdomen and gluteal region do not exhibit lipoatrophy but rather accumulate excess adipose tissue.(13) With the exception of hepatomegaly, metabolic complications are rarely seen in association with APL.(22)

Table B5: Essential features of PL

Type	FPL	APL
Adipose tissue distribution		
Mean age of onset	9.9 years (range 0–16)	8.2 years (range 0.5–16)
Male:female ratio	1:1–2	1:4–5
Essential characteristics	Regional loss of adipose tissue, usually around puberty, may resemble obesity or Cushing's Syndrome	Gradual loss of adipose tissue from head downwards, fat accumulation around the hips, buttocks, legs
Abbreviations: APL, acquired partial lipodystrophy (Barraquer-Simons syndrome); FPL, familial partial lipodystrophy (Dunnigan type or Köbberling type); PL, partial lipodystrophy		

Source: Handelsman, 2013 (19); Brown, 2016 (2); Gupta, 2017 (16)

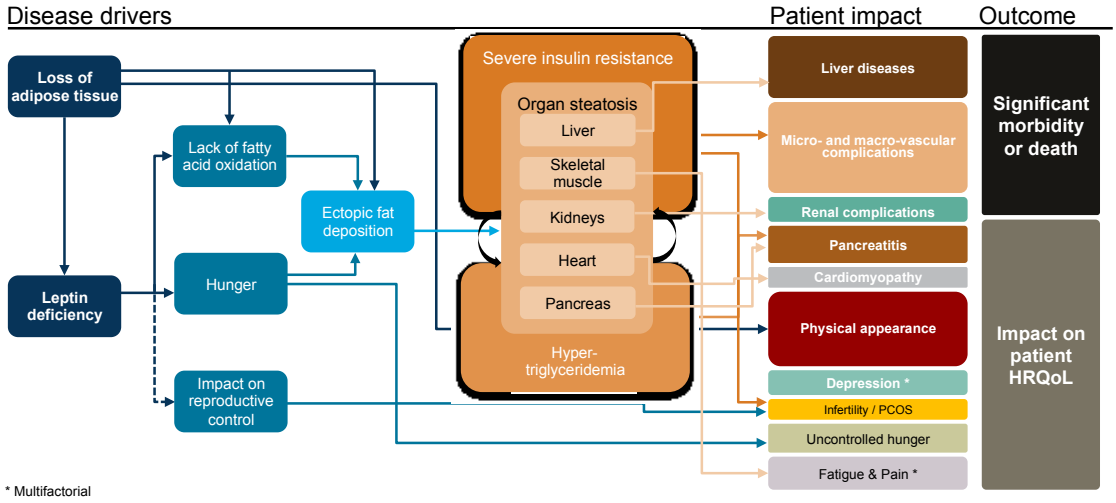
Patients with PL have variable fat loss, and their leptin levels can range from low to normal.(23) They show a more heterogeneous disease profile than patients with GL, with an increased variability in the severity of metabolic abnormalities. The expected indication for metreleptin in PL patients (and therefore the focus of this dossier) includes the group of patients with more severe metabolic abnormalities regardless of standard treatment and lower leptin levels, the final criteria for which is yet to be defined.(1)

6.1.2 Underlying course of the disease

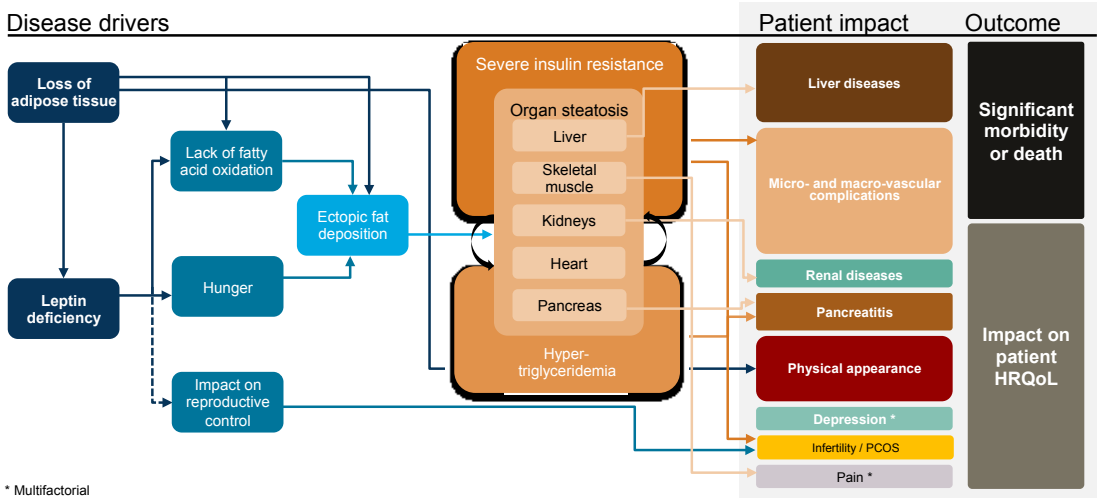
A schematic of the disease course of GL and PL is shown in Figure B1.

Figure B1: The disease course of (A) GL and (B) PL

(A)



(B)*



Abbreviations: , generalised lipodystrophy; HRQoL,health-related quality of life; PCOS, polycystic ovary syndrome; PL, partial lipodystrophy

* In PL patients, disease burden is especially high in a subset of patients with PL with more severe metabolic abnormalities

Source: Aegerion, created from expert input and a review of the literature

The disease drivers are loss of adipose tissue, together with the resultant leptin deficiency. Subcutaneous adipose tissue loss is a primary feature of LD, regardless of the subtype. CGL patients have a complete lack of adipose tissue from birth or infancy (

Figure B1A).(2) FPL is characterised by subcutaneous adipose tissue loss in the limbs, buttocks and hips (

Figure B1B).(21) Leptin is primarily produced by white adipose tissue and correlates positively with body fat, reflecting the number of energy stores.(24) Via a complex neural circuit, leptin promotes satiety (the feeling of feeling full), leading to decreased food intake.(25) Leptin also acts peripherally to decrease gluconeogenesis in the liver and adipose tissue and to increase glucose utilisation in skeletal muscle by activating signalling pathways which overlap with, but are not identical to, those of insulin.(26) Finally, leptin may protect peripheral tissues from lipotoxicity by stimulating fatty acid oxidation, as it has been shown to reduce intrahepatic and intra muscular lipid accumulation.(27) A deficiency in leptin can therefore result in insatiable hunger, increased gluconeogenesis and reduced fatty acid oxidation.

Hyperphagia caused by leptin deficiency leads to increased food intake resulting in ectopic fat accumulation and organ steatosis in patients with LD. This is particularly evident in the liver, kidneys, skeletal muscle, heart and pancreas, where lipid deposits impact the functioning of the organs.(13) The liver becomes a major repository for excess triglycerides beyond a normal range in volume which results in hepatic steatosis and steatohepatitis.(21)

Hypertriglyceridemia is often severe in patients with GL and PL (with serum triglycerides often elevated in the range of 1,000 mg/dL [11.29 mmol/L] compared with normal levels of 150 mg/dL [1.69 mmol/L]).(28) This elevated level is not readily amenable to treatment with conventional lipid-lowering agents, predisposing patients to serious conditions such as acute pancreatitis, which can be life-threatening. In addition, elevated triglyceride levels are also a known risk factor in cardiovascular disease.(29) A prospective cohort study of 13,981 people in the general population in Denmark followed from baseline (1976-1978) until 2004 found that the risk of myocardial infarction, ischaemic heart disease and death was significantly increased with every 1 mmol/L increase in triglyceride levels.(29)

The accumulation of ectopic fat throughout the body is associated with severe insulin resistance in patients. Insulin resistance leads to a host of conditions including diabetes, hypertriglyceridemia, polycystic ovarian syndrome (PCOS), and non-alcoholic fatty liver disease (NAFLD).(2) Severe insulin resistance results in the development of hyperglycaemia, which can be measured by HbA1c. In the healthy population HbA1c levels are less than 6%, while with patients with LD HbA1c levels can be in excess off 8.5%.(30, 31) A diagnostic indicator of diabetes is HbA1c levels of greater than 6.5%.

6.1.3 Disease morbidity and mortality

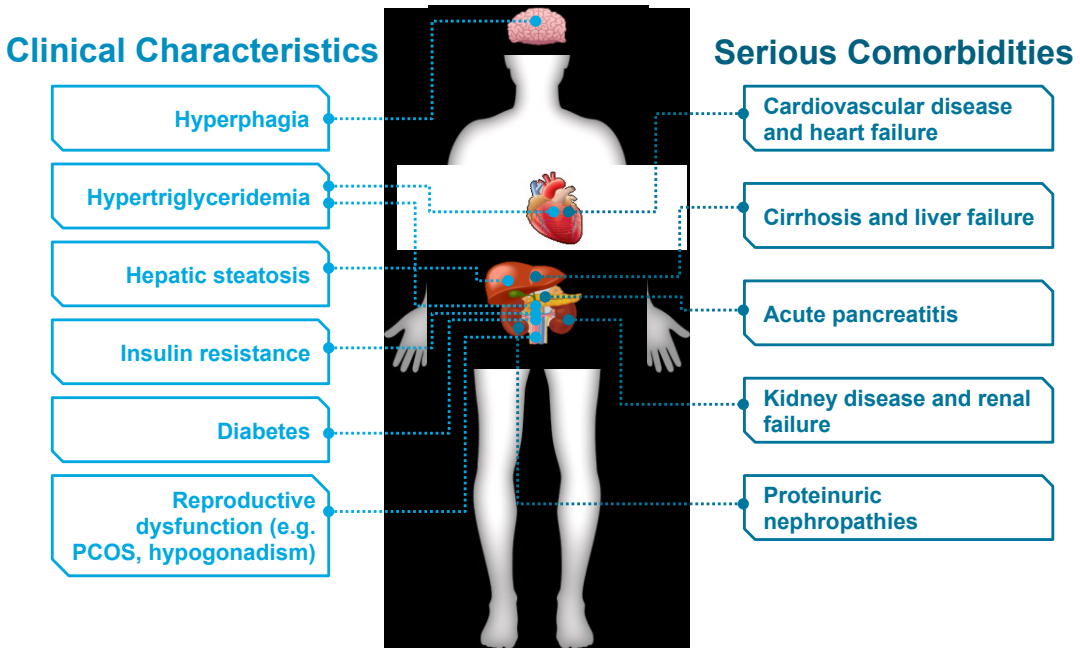
The disease course of GL and PL leads to severe morbidity for patients, with multi-organ involvement from an early age (Figure B2). Metabolic abnormalities lead to a host of co-morbidities, many of which are life-threatening.(16, 32-35) The severe metabolic abnormalities associated with GL occur at a young age and may result in

premature diabetic nephropathy, retinopathy, cardiomyopathy, recurrent attacks of acute pancreatitis, hepatomegaly, and organ failure.(19, 34)

Akinci et al. described the natural history of patients with CGL based on the Turkish Lipodystrophy Study Group.(32) The study highlighted the early onset of severe metabolic complications in these patients. As a consequence, these patients also develop end-organ complications resulting in cirrhosis and end-stage renal disease (ESRD) requiring organ transplantation. Additionally, the risk of premature death due to cardiovascular disease was high in these patients.(32)

Lima et al. reported on patients with CGL who were followed over 17 years at a single centre.(35) Over two-thirds of patients had diabetes with onset in the teenage years; mean duration of diabetes in the overall group was 12 years. Almost half of the patients were on insulin.(35)

Figure B2: The metabolic complications and disease burden of GL and PL



Abbreviations: GL, generalised lipodystrophy; PCOS, polycystic ovary syndrome; PL, partial lipodystrophy

Source: Handelsma,n 2013 (19); Brown, 2016,(2); Gupta, 2017,(16); Garg, 2011 (34)

6.1.3.1 Micro- and macro-vascular complications

Elevated triglyceride and ectopic fat distribution contribute to micro- and macro-vascular complications. Elevated triglyceride levels are a known risk factor for cardiovascular disease. In the Copenhagen City Heart Study, which was initiated in 1976 and has followed 19,329 subjects, each 1 mmol/L increase in triglycerides is

associated with a 40% increase in risk for myocardial infarction, a 25% increase in risk for ischemic heart disease, and an 18% increase in risk of death in women, and 16%, 12%, and 10% increased risks, respectively, in men, when adjusted for age and HDL-C.(29)

Cardiomyopathy has been reported to occur in 20% to 55% of patients with GL and is a significant cause of morbidity from cardiac failure and early mortality at approximately age 30 years.(36) Many patients with FPL die of coronary heart disease or cardiomyopathy and rhythm disturbances.(34) Cardiovascular complications occur with increased prevalence and earlier onset in patients with FPL, with atherosclerotic vascular disease occurring in 45% to 53% of females with FPL compared with 0% to 15% of unaffected family controls in two separate studies.(37, 38) The rate of hospitalisation for coronary artery bypass grafting in patients with FPL was approximately 3 orders of magnitude higher than that in the general population for the same age range and gender (1 in 3.75 vs. 1 in 7,350).(37)

6.1.3.2 Renal failure and pancreatitis

Severe insulin resistance leads to patients with GL and PL developing acute pancreatitis, cirrhosis, ESRD requiring renal transplantation and blindness due to diabetic retinopathy.(34) Chronic renal disease and membranoproliferative glomerulonephritis (MPGN) can occur in patients with GL and PL due to longstanding, suboptimal controlled diabetes. Approximately one-fifth of patients with APL will develop MPGN,(34) which can be fatal in some patients.(22)

Additionally, one of the primary concerns with hypertriglyceridaemia, especially when triglyceride levels exceed 1,000 mg/dL (11.29 mmol/L), is the risk for acute pancreatitis which can be life-threatening with a high mortality rate of 40% to over 50% when accompanied by complications like infection or organ failure. In the pivotal study NIH 991265/20010769, 31% of patients reported a history of pancreatitis (33 of 107).(31)

6.1.3.3 Liver disease

Ectopic fat distribution leads to complication in the functioning of the liver, with cirrhosis and NAFLD being associated with GL and PL.(2) Liver failure, gastrointestinal haemorrhage, hepatocellular carcinoma have also been identified as major cause of mortality amongst patients with GL and PL.(2, 34)

In a review of 79 patients with AGL, 84% had hepatomegaly, which can progress to steatohepatitis, cirrhosis, and liver failure.(22) In this review, 60% of patients with AGL had elevated alanine aminotransferase (ALT) levels, mostly due to hepatic steatosis or steatohepatitis.(22) Non-alcoholic steatohepatitis (NASH) is highly prevalent in patients with LD,(21) and there are no treatment options current available to treat this condition.

6.1.3.4 Insatiable hunger and hyperphagia

Low leptin levels act on the brain as a starvation signal, and therefore patients with LD tend to have insatiable hunger and hyperphagia. Hyperphagic LD patients have a constant feeling of starvation – they cannot stop eating, waking up to eat, and are constantly fighting for food.(39) Reflecting that the need for food (response to hunger) is one of the most basic of human needs (40), hyperphagia significantly impacts the QoL of affected individuals and also their families/carers (see Section 7.1).

As described, hyperphagia is also a key driver of the morbidity associated with LD (Section 6.1.2; Figure B2). Patients with LD cannot store excess calories in their adipose tissue, and instead they are deposited as ectopic fat in the liver and muscle, causing severe insulin resistance, diabetes mellitus, hypergtriglyceridaemia, and steatohepatitis.(13, 21)

Hyperphagia also impacts on the treatment and management of LD. Patients must undergo diet modifications to manage the metabolic complications underlying the disease, however dietary restriction may be challenging to achieve in some patients due to hyperphagia.(2, 39) In addition, in children food restriction must be balanced by requirements for growth.(2) Furthermore, current conventional therapies used in the management of LD have no effect on the insatiable hunger and the hyperphagia, and there is therefore a high unmet need for an effective treatment of this key aspect of the disease.

6.1.3.5 Fatigue and pain

Patients may also experience fatigue and pain due to the metabolic anomalies as part of the disease course. In a review of 16 case reports of patients with AGL treated at a single treatment centre in the US, patients presented with pain at diverse sites. While no quantitative data were gathered, pain was reported in knee joints, abdomen, calf muscle and skin by one patient each.(17) The cases noted that the diverse pain could be attributed to a number of different underlying causes in the LD disease course. For example, one patient presented with pain in the calf muscle, which was suggestive of intermittent claudication. Another patient developed painful skin lesions over her legs and thighs alongside abdominal pain. An additional patient had pain in both knee joints, while loss of plantar fat in the feet was associated with the development of “painful” callosities, which limit movement.(17) In addition, one patient reported general fatigue in these patient case reports.(17) Abdominal pain has also been reported by patients with GL and PL, which can be attributed to hypertriglyceride levels in patients.(41)

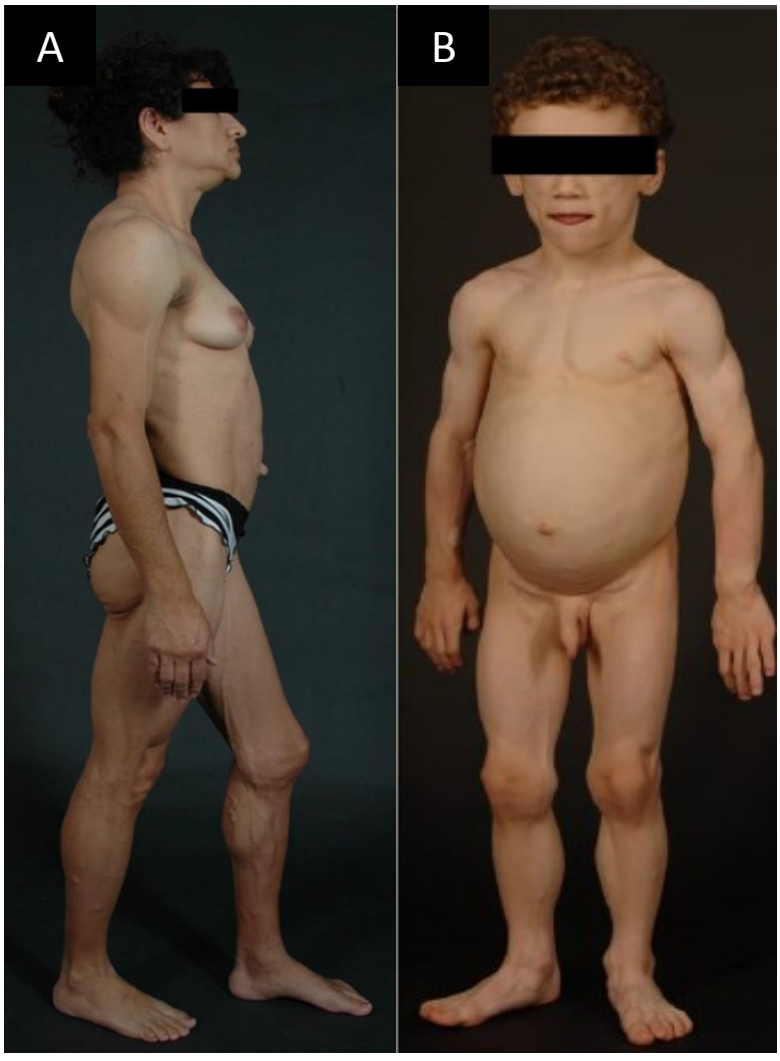
6.1.3.6 Physical appearance

The partial and generalised loss of subcutaneous fat as well as the fat abnormal fat distribution can have marked effect on the physical appearance of patients with GL and PL. In CGL, patients may have prominent muscles, phlebomegaly, acanthosis nigricans, and umbilical prominence.(2) In **Error! Not a valid bookmark self-**

reference. the patient, a 33-year old Hispanic female with CGL, has generalised loss of subcutaneous fat with acanthosis nigricans in the axillae and neck. The patient also has umbilical prominence and acromegaloid features (enlarged mandible, hands, and feet).(2)

In AGL, in addition to the physical appearance of CGL, patients may have severely reduced adipose tissue loss from the palms, soles, and intraabdominal area.(13) In **Error! Not a valid bookmark self-reference.**, the patient had severe loss of subcutaneous fat with marked acanthosis nigricans in the neck, axillae and groin.(2)

Figure B3. The physical appearance of (A) a 33-year old female with CGL and (B) 8-year old male with AGL

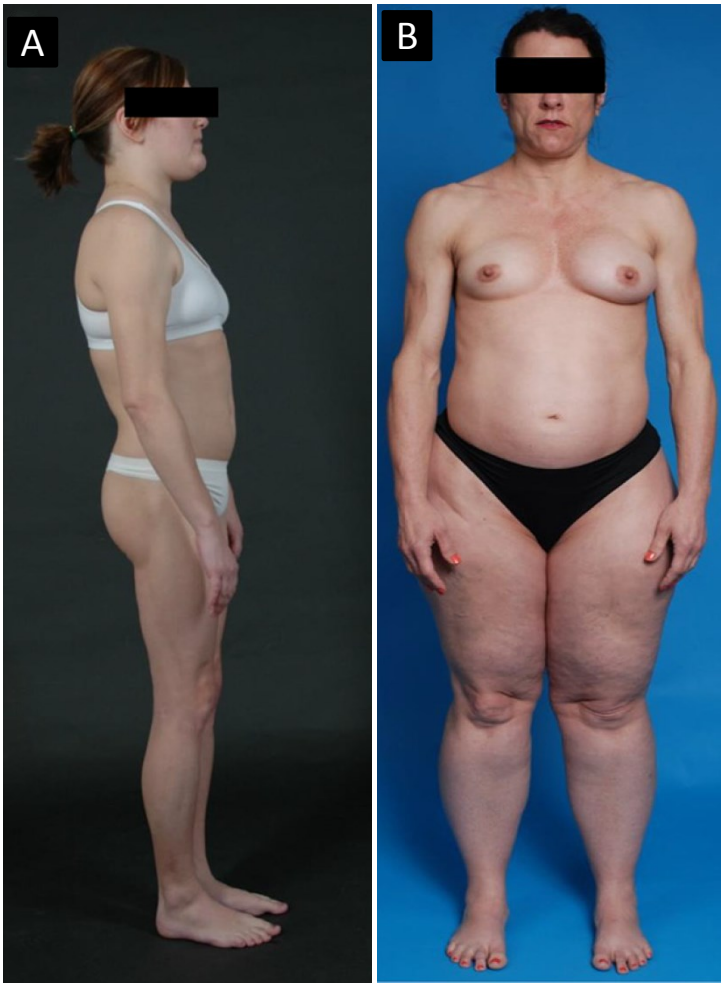


Abbreviations: AGL, acquired generalised lipodystrophy; CGL, congenital generalised lipodystrophy

Source: Brown, 2016 (2)

The loss of subcutaneous adipose tissue in FPL can affect the appearance of the limbs, buttocks and hips. Additionally, excess fat accumulation, which varies by FPL subtype, may result in a Cushingoid appearance (including facial roundness).(2) In Figure B4A, the patient is a 26-year old female with FPL of the Dunnigan subtype. The patient has marked fat loss of subcutaneous fat from the upper and lower extremities and accumulation of fat in the face and chin.(2) The distinguishing physical features of APL include cephalocaudal progression of fat loss. Fat loss begins in the face and subsequently spreads to the neck, upper extremities, thorax and abdomen. In Figure B4, the patient, a 45-year-old female with APL (Barraquer-Simons syndrome), had marked loss of subcutaneous tissue from the face, neck, upper extremities, and chest but had increased fat accumulation in the lower extremities.(2)

Figure B4: The physical appearance of (A) a 26-year old female with FPL and (B) a 45-year old female with APL



Abbreviations: APL, acquired partial lipodystrophy; FPL, familial partial lipodystrophy
Source: Brown, 2016 (2)

6.1.3.7 Depression and neurological affects

The disease course of LD may have negative consequences for patients' psychological health. Physical dysmorphia, insatiable hunger and hyperphagia, infertility, fatigue and pain may contribute to depression in patients. In a survey of LD experts in Europe, depression was considered to be of clinical importance and, anecdotally, occurs at a medium-high frequency amongst patients with GL and PL.(42)

Physical dysmorphia due to LD has been shown to contribute to the psychological distress of patients who often resort to corrective measures including plastic surgery, e.g., muscle tissue transfer or autologous fat grafts, as well as dermal fillers.(2)

Additionally, neurological deficits may also occur in GL and PL. Intellectual disability has been reported in 50% of patients with AGL, 47% in patients with CGL 43% in patients with FPL and 8% in patients with APL, respectively.(16)

6.1.3.8 Infertility and PCOS

Leptin is one of the hormones that contributes to sexual maturation and patients with LD have been shown to have delayed puberty and hypergonadotropic hypogonadism (also known as primary or peripheral/gonadal hypogonadism, whereby sex steroid production is lacking leading to delayed or absent puberty and infertility).(43) As a result, infertility and PCOS are common in women with GL,(2, 13) and successful pregnancy is extremely rare.(34) Females commonly present with clitoromegaly, hirsutism, amenorrhea or irregular menstrual cycles, and ovarian cysts.(13, 21)

Female patients with PL also have an elevated risk for many reproductive abnormalities including PCOS and infertility compared with the general population.(42) A clinical follow-up of seven families with patients with FPL due to LMNA found that 54% of the women with LMNA mutations exhibited clinical PCOS phenotypes, 27% had infertility, 50% experienced at least one miscarriage, 36% developed gestational diabetes and 14% experienced eclampsia and foetal death.(42) In the general population, 4.8% of women have PCOS, 10% have infertility, 10.1% experience at least one miscarriage, 5–10% have gestational diabetes and 2.6% experience eclampsia and foetal death.(42)

6.2 Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year, and provide the source of data.

There is limited published data available on the incidence and prevalence of LD in England. One study (Chiquette et al. 2017) identified in the literature search was considered but was not deemed accurate or generalisable for a UK population and the anticipated metreleptin licence (see Section 13.8).(11) More relevant and accurate estimates are available based on EAP data from a decade of metreleptin use in UK clinical practice at Addenbrooke's.

There are currently [redacted] LD patients receiving metreleptin at Addenbrooke's under the EAP – [redacted]. Of these patients, some may have initiated metreleptin over a decade ago since the beginning of the EAP. As the EAP has been running for over 10 years it is expected that the number of patients on the programme is a good indicator of the number of eligible patients in the England. Clinicians from Addenbrooke's Hospital in England who are involved in the UK EAP have been consulted to provide an estimate of the number of new GL and PL patients each year who would be eligible for metreleptin. Based on expert clinical opinion, it is assumed that [redacted] new patients each year would be eligible for metreleptin treatment ([redacted]).

Please see Section 13 for the estimated number of new patients eligible for metreleptin in England over the next 5 years.

6.3 Please provide information about the life expectancy of people with the disease in England and provide the source of data.

The complications of LD can have catastrophic consequences leading to premature mortality, occurring at young ages in some cases. There are no natural history studies of LD patients in England (or the UK) to inform on the life expectancy of people with the disease in England. An interim analysis from the EAP is expected in Q1/Q2 2018. However, a SLR and data synthesis of a very large number of patients with LD in the context of a rare disease (i.e. CGL=519; AGL=86; FPL=124; and APL N=124) conducted by Gupta et al reported on mortality of LD patients from around the world (Figure B6).(16) The mean age of mortality was 12.5 years for CGL, 32.2 years for AGL, 27.8 years for FPL and 22.7 years for APL. The causes of death included organ failure (including liver, renal and cardiac failure), respiratory infection and sepsis.

Table B6: Mortality in LD patients

Study group	n/N[a] deaths (%)	Age at mortality mean (SD)	Cause of death (n)
CGL N=519	33/502 (0.2)	12.5 (11.3)	Acute liver failure (1), peritonitis (1), respiratory infection (6), renal failure (1), cardiac failure (3), multi-organ failure (1), epilepsy (2), not reported (18)
AGL N=86	9/84 (10.7)	32.2 (28.3)	Acute liver failure (2), respiratory infection (1), hepatocellular carcinoma (1), gastrointestinal haemorrhage (1), brain tumour (1), not reported (3)
FPL N=124	7/98 (7.1)	27.8 (26.9)	Renal failure (1), cardiac failure (1), aspiration (1), sepsis (1), not reported (3)

APL N=124	3/124 (2.4)	22.7 (18.5)	Renal failure (1), cardiac failure (2)
Abbreviations: AGL, acquired generalised lipodystrophy; APL, acquired partial lipodystrophy; CGL, congenital generalised lipodystrophy; FPL, familial partial lipodystrophy [a] Patients whose mortality status was known at reporting			

Source: Gupta, 2017 (16)

7 Impact of the disease on quality of life

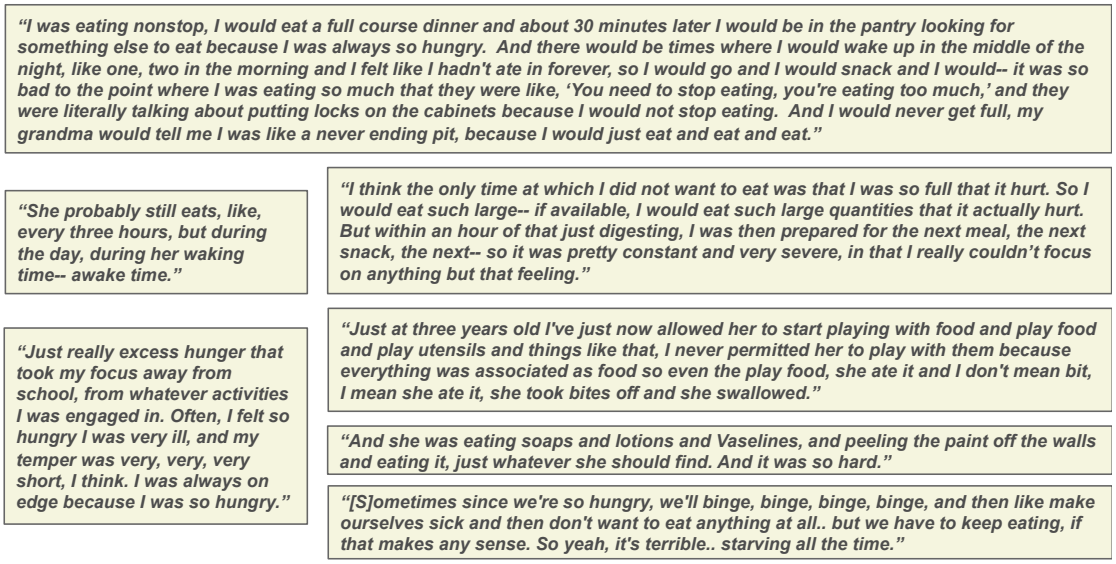
7.1 Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).

The impact of LD on the QoL of patients, and their cares/families can be devastating. However, there has been a paucity of published studies evaluating the health related QoL (HRQoL) of patients with LD and their carers. A SLR described in Section 10.1.5 identified only one study reporting on the HRQoL. Dhankar et al. (2015) evaluated the HRQoL in LD patients from the Lipodystrophy Connect Registry and reported that the average estimated EQ-5D score associated with LD was 0.67 (SD: 0.11), much lower than the average EQ-5D of a general population (0.866) (see Section 10.1.6 for more details).(44)

Interviews with patients with LD conducted at the NIH in the US on behalf of Aegerion demonstrates the negative impact of LD.(45)

Hyperphagia, characterised by the ever-present pursuit of food, is a relentless, overwhelming burden for patients.(46) Patients are highly constrained by food access issues, impacting on many aspects of their daily lives including attending school, work and social situations (Figure B5). Patients also suffer from mood and sleeping problems (Figure B5). The extreme level of food seeking additionally creates stress on families/carers. Carers may need to provide 24/7 supervision, especially as patients may also consume inappropriate or non-food items (Figure B5). Hyperphagia can lead to disruptive activity in young children, which can be socially isolating for their carers. Of note, the negative impact of hyperphagia in the context of another rare disease, Prader-Willi syndrome, has been documented in the literature.(46-49)

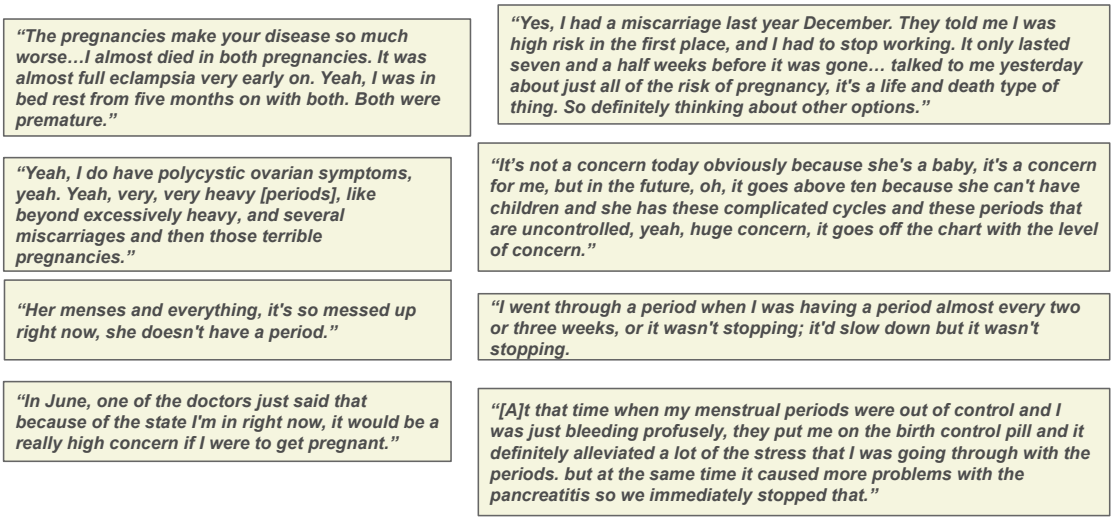
Figure B5: Selected quotes in LD patients and carers: Hyperphagia



Source: Data-on-file (45)

Female LD patients can suffer reproductive dysfunction as a result of leptin deficiency and severe insulin resistance. The adverse impact of reproductive dysfunction in females in the general population, including PCOS, infertility and miscarriage are well documented. For example the spectrum of the symptoms of PCOS such as hirsutism, skin problems, menstrual problems and finally infertility has a huge negative impact on the individuals' psychological and interpersonal functioning. PCOS symptoms can lead to significant deterioration in QoL and be highly stressful negatively affecting psychological well-being and sexuality.(50) Following miscarriage, women can experience post-traumatic stress, anxiety and depression.(50, 51) Following miscarriage, women can experience post-traumatic stress, anxiety and depression.(51) The experience of pregnancy loss and infertility can also have a considerable impact on partners. The interviews with patients with LD confirm the impact of reproductive dysfunction in the context of LD (Figure B6).

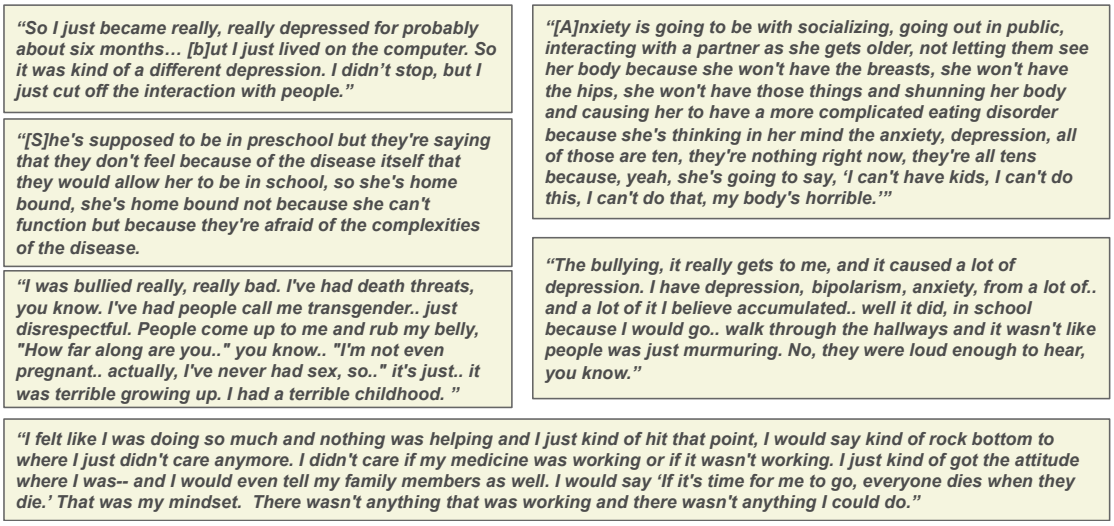
Figure B6: Selected quotes in LD patients and carers: Reproductive dysfunction



Source: Data-on-file (45)

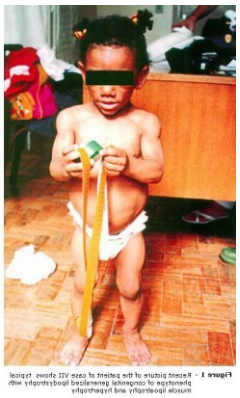
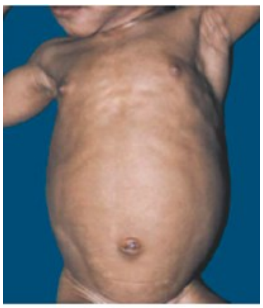
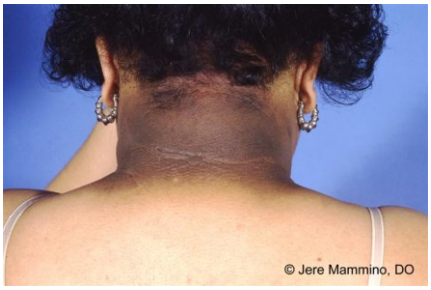
Patients with LD can experience anxiety and depression due to the clinical burden of the disease including impaired physical appearance (which can be associated with bullying and low self-esteem), hyperphagia, reproductive dysfunction, fatigue and chronic pain (see Figure B7 for selected quotes and Table B7 for examples of the physical impact of LD). Furthermore, low leptin levels are associated with increased symptoms of depression, independent of body fat or weight.(52)

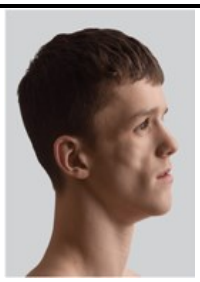
Figure B7: Selected quotes in LD patients and carers: Anxiety and depression



Source: Data-on-file (45)

Table B7: Illustrations of physical impact of LD

Physical Impairment	Example
Extreme muscularity of arms and legs	
Hepatomegaly, abdominal distension	
Excessive facial hair	
Acanthosis nigricans	
Skeletal facial features	

	
Severe body asymmetry with lipodystrophic arms and legs and fat accumulation in face and neck typical of Dunnigan syndrome (picture B) or, differentially, LD in face, neck, thorax and arms with fat accumulation in hips that can be seen in some Barraquer-Simmonds syndrome (picture D)	
Abbreviations: LD, lipodystrophy	

Other symptoms such as fatigue (Figure B8) and frequent infection/illness (Figure B9), in addition to hyperphagia and anxiety/depression, can lead to impaired or complete inability to work or attend school, as well as to social isolation. In turn members of the family may not be able to work or socialise due to caring responsibilities.

Figure B8: Selected quotes in LD patients and carers: Fatigue

"I'm not able to work and make a living wage that I-- or exceed, by far, a living wage that I should have. I mean, that's a huge impact."	*"I would say the biggest impact is that I'm not able to live a full schedule. My fatigue is great enough where I really limit activities. So if I spend time with my kids on Saturday, I'm going to have to rest on Sunday."*
"She has no energy to drink even like two ounces of milk in the bottle. So that was the very first symptom that she was very, very sick."	*"Fatigue.. very fatigued…I'm very fatigued."*

Source: Data-on-file (45)

Figure B9: Selected quotes in LD patients and carers: Compromised immune system and infections in LD

"Anything. A virus, viral infections that just lasted forever, the flu, whatever was going around, just a really compromised immune system."	*"[S]he was sick all the time and it was always like pneumonia, pneumonia, pneumonia. She's had pneumonia I can't tell you how many times."*
"So we deal with the fevers and colds a lot, her immune system is severely compromised and so can't be around people."	*"[I]mmune system is so compromised, it's insane. We fight a lot of respiratory issues. Right now, we're fighting with a croup."*

Source: Data-on-file (45)

A summary of the impact on QoL associated with LD is shown in Table B8. Overall, this is a population to whom an effective therapy has the potential for a profound positive effect on lifestyle opportunities (including working and attending school) and QoL of patients and carers.

Table B8: Range of complications and impact on QoL associated with LD

Complication	Clinical features	Potential impact on QoL
Glucose control	• Diabetes (and associated symptoms/sequelae) • Insulin resistance	• Need for extra medication (e.g. diabetes) • Very high insulin requirements • Increased risk of cardiovascular disease • Higher mortality risk • Organ damage • Diabetes complications such as nerve damage, amputation, etc.
Triglycerides control	• Hypertriglyceridaemia • Hypercholesterolaemia	• Need for extra medication (e.g. hypertriglyceridaemia) • Organ damage • Increased risk of stroke, heart disease and heart attack • Higher mortality risk
Impaired physical appearance	• Extreme muscularity of arms and legs • Excessive facial hair • Acanthosis nigricans • Skeletal facial features • Severe body asymmetry (swollen face vs. skinny/muscular legs)	• Low self-esteem • Depression • Need for aesthetic/restorative surgery
Female reproductive dysfunction/infertility	• Partially or completely compromised female reproductive function • Missed or irregular menstrual cycles, which can be associated with heavy bleeding • Ovarian cysts, PCOS • Clitoromegaly • Ovaries produce more male hormones than normal • Physical signs (acne, male-pattern baldness, weight gain, skin tags)	• Inability to have children • Anxiety/depression • Delayed puberty
Hyperphagia	• Uncontrollable, constant hunger • Excess food intake • Damage to organs from excess fat deposit	*"…My daughter is unable to attend public schooling… Her inability to sit and/or stand for long periods of time along with her excessive*

Complication	Clinical features	Potential impact on QoL
		appetite and needs to eat every hour or so would cause a disruption to class"
Liver damage	• Ectopic fat deposit on liver • Hepatomegaly • Hepatic steatosis • Steatohepatitis • Cirrhosis • Liver failure	• Loss of weight and appetite • Extreme fatigue, weakness • Hallucinations, confusion or trouble concentrating • Vomiting of blood • Higher mortality risk
Heart damage	• Cardiomyopathy • Heart failure • Myocardial infarction • Arrhythmia	• Need for surgery • Early death • Chest pain (angina) • Need to take regular medications
Kidney damage	• Chronic kidney disease • Nephropathy • Kidney failure	• Need to be put on dialysis • Need for kidney transplantation • Higher mortality risk
Pancreas damage	Acute pancreatitis	• Need for extra medication (e.g. diabetes, pancreatitis) • Abdominal pain • Severe pancreatitis harming other vital organs • Higher mortality risk
Retinopathy	• Impairment or loss of vision due to damage to retina blood vessels • Typically a complication of diabetes	• Blurred vision • Blindness • Impaired social/work functioning

Complication	Clinical features	Potential impact on QoL
Neuropathy	• Peripheral nerve damage • Typically a complication of diabetes	• Abnormal sensation in feet and hands • Pain not easily managed with common analgesics • Impaired muscle movement
Amputation	• Common feet extremity amputations • Typically a complication of diabetes	• Impaired mobility • Grief over lost limp/depression
Chronic pain	• Frequent abdominal pain • Musculoskeletal pain in areas of pressure (buttocks, soles) due to lack of fat cushions	• Increased stress • Continual discomfort • Depression • Fatigue • Trouble sleeping • Weakness/lack of energy • Need for mediation for temporary alleviation of symptoms
Ability to perform work/school work	Impaired or complete inability to work or attend school due to: • Fatigue • Hyperphagia • Bullying (e.g. due to physical appearance) • Frequent infection/illness	• Low wages/poor work prospects • Need to take unpaid leave • Inappropriate socialisation • Depression/anxiety
Depression	• Impaired physical appearance • Hyperphagia • Chronic pain	*"I felt like I was doing so much and nothing was helping and I just kind of hit that point, I would say kind of rock bottom to where I just didn't care anymore. I didn't care if my medicine was working or if it wasn't working. I just kind of got the attitude where I was-- and I would even tell my family members as well. I would say 'If it's time for me to go, everyone dies when they die.' That was my mindset. There wasn't anything that was working and there wasn't anything I could do." (Patient experience pre-metreleptin)*
Abbreviations: LD, lipodystrophy; PCOS, polycystic ovary syndrome; QoL, quality of life		

7.2 Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.

Metreleptin treatment is effective at improving metabolic abnormalities associated with LD, both in the short-term and long-term. Many of these changes have the potential to substantially improve the QoL of patients and their carers.

Metreleptin has been shown to improve metabolic status (e.g., high triglyceride and HbA1c levels unresponsive to other treatments). In the pivotal study NIH 991265/20010769 clinically meaningful and statistically significant improvements in HbA1c consistent with improvement in insulin sensitivity were demonstrated: mean actual change in HbA1c to Month 12 was -2.2% ($p<0.001$) for GL patients and -0.9% ($p<0.001$) for patients in the PL subgroup (i.e. corresponding to the sought after indicated PL population). Reductions of this magnitude in HbA1c are associated with significant reductions in clinical complications associated with hyperglycaemia. Results of the UK Prospective Diabetes Study (UKPDS) conducted in over 4500 patients showed that each 1% reduction in HbA1c was associated with a statistically significant 21% reduction in risk of death due to diabetes, 14% reduction in risk for myocardial infarction, and 37% reduction in risk for microvascular complications. As a reference for the changes in HbA1c observed with metreleptin treatment, mean changes in HbA1c after 24 weeks of sitagliptin monotherapy in patients with type 2 diabetes were -0.5% to -0.6% and when administered in combination with metformin, were -0.7% to -1.4%.(53) Metreleptin should therefore be associated with reductions of the micro- and macrovascular complications associated with diabetes, improving the QoL of patients.

Elevated triglyceride levels are a known risk factor for cardiovascular disease and pancreatitis. Metreleptin was associated with clinically meaningful and statistically significant improvements in hypertriglyceridaemia: the mean percent change in triglycerides to Month 12 was -32.1% ($p=0.001$) for the GL group and -37.4% ($p<0.001$) in the PL subgroup (excluding one outlying noncompliant patient).(53) These improvements in triglyceride levels are likely to reduce the risk of developing cardiovascular disease and pancreatitis.

The improvements in HbA1c and triglycerides occurred in some patients in conjunction with reductions or even discontinuation of the use of antidiabetic medications (insulin, orally administered agents, or both) and/or lipid lowering medications, thus reducing the burden of diabetes and/or hypertriglyceridaemia management, both on the patient (e.g. reducing pill burden) and the health service.

Overall, the improvements were sustained over long-term treatment – most patients received 2 or more years of therapy with a maximum duration of 14 years.

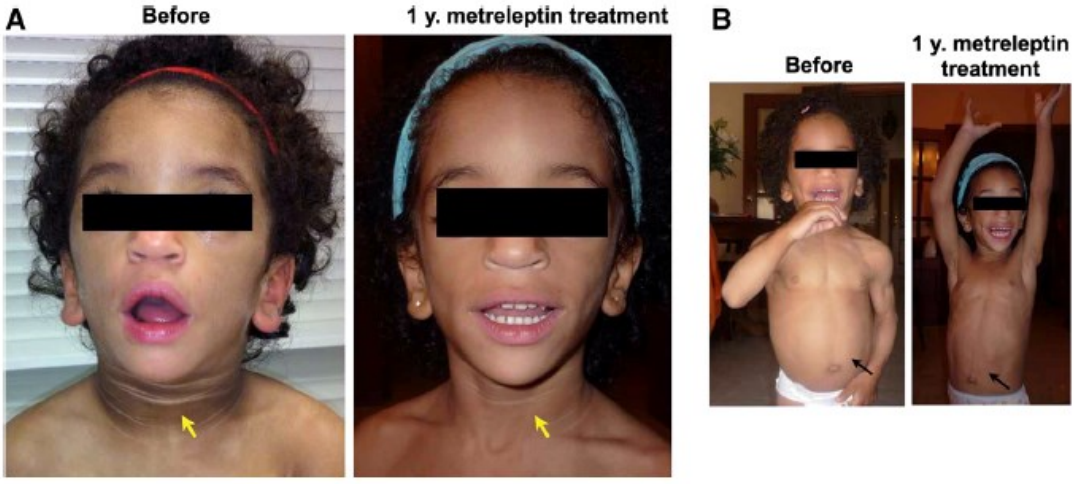
Metreleptin can also improve appetite regulation, with patients experiencing a sense of satiety or satiation.(54, 55) Improvement in hyperphagia helps to break the cycle of excess food consumption that further exacerbates metabolic abnormalities as ingested fats are directed towards ectopic locations. It also has the potential to vastly improve the QoL of patients and carers.

Metreleptin is also associated with improvements in LD-associated liver disease. NASH, a frequent condition LD patients, is commonly associated with elevated liver function tests, and therefore measurements of the liver enzymes ALT, aspartate aminotransferase (AST), and liver volume are useful surrogates for this condition. Metreleptin is associated with reductions in ALT and AST and liver volume.(9, 10, 56-58) Significant improvements in steatosis, ballooning injury and NASH scores have also been reported.(57, 58)

Metreleptin has been shown to halt or in some cases reverse organ damage associated with LD. In females, metreleptin has normalised gonadotropin secretion, leading to normal progression of puberty, normalisation of menstrual periods and improved fertility.(2, 43, 59, 60)

Improvements in the physical appearance of LD patients have also been noted, including improvements in facial fat deposition, improvements in acanthosis nigricans and having a less prominent abdomen and decreased girth (Figure B10).(56, 61, 62)

Figure B10: Effect of metreleptin on a young girl (age 23 months old) with regard to (A) acanthosis nigricans and (B) hepatic steatosis



Arrows show the improvement in (A) the skin lesions and (B) the reduction in abdominal circumference

Source: Araujo-Vilar, 2015 (56)

Overall, metreleptin is anticipated to mitigate the clinical and QoL impact, as well as the cost to the NHS and personal social services (PSS), associated with patients' metabolic disorders, progressive organ damage, physical appearance, hyperphagia, female reproductive dysfunction, pain, and depression.

Extent and nature of current treatment options

8 Extent and nature of current treatment option

8.1 Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.

Aegerion are not aware of any NICE clinical guidelines, NICE pathways or published national guidelines on the management and treatment of LD.

8.1.1 NHS England Service Specification (A03/S(HSS)/b)

NHS England established a service specification in 2013 (A03/S(HSS)/b).(8) The service is targeted at patients with LD and/or extreme insulin resistance. The service specification explicitly notes that these are very rare but metabolically devastating disorders associated with significant long-term morbidity and mortality.

The National Severe Insulin Resistance Service provides a multidisciplinary outpatient clinic at Addenbrooke's hospital (CUH) plus inpatient stays for initiation of therapy when indicated. As part of an EAP, treatment with metreleptin in England is currently provided at this centre, where there the service specification (A03/S(HSS)/b) in place. The aim of the service is to provide diagnostic, therapeutic and educational support for both patients and their local clinical carers, and to establish and disseminate evidence-based recommendations for the therapy of this severe group of conditions. An overview of the service specification with a focus on patients with LD is shown in Table B9.

Table B9: Overview of the NHS service specification for patients with LD

Diagnosis	• Accurate clinical assessment is an essential step to putting the correct management strategies in place early for this group of patients. This requires close links to clinical biochemistry, molecular genetics and radiology services, to provide a complete, integrated package of clinical, biochemical and radiological evaluation as well as definitive molecular genetic diagnosis where appropriate. • Objective: To provide a specific diagnosis to all patients with LD/severe insulin resistance. This is not currently possible as the genetic basis of several of the disease subtypes remains unknown but there is an aspiration to meet this objective in due course.
Patient Management	• Where good metabolic control is maintained in referred patients, patient management will be delivered through annual reviews in the national service in conjunction with locally commissioned diabetes care • The nationally commissioned service will also provide a limited amount of specialist dietetic and nursing care directly

	to patients and by providing expert advice to local diabetes services. • Expertise in the use of leptin is essentially only available through the nationally commissioned service within the UK. • Where specialist therapies are introduced, several reviews at CUH per year may be required and will be undertaken in conjunction with local diabetes care where appropriate.
Overview of the service	• The core element of service provided is a weekly multidisciplinary clinic consisting of (minimum requirement): consultant; specialist nurse; dietician; genetic counsellor (only a strict requirement for all cases with a new genetic diagnosis and after that the genetic counsellor will be available according to individual patient requirements). Patients presenting before the age of 16 years will be seen in conjunction with paediatric endocrine consultants supported by paediatric specialist nursing and dietetic input. • Liaison with local clinicians managing the patients is a key component of the service outside the weekly multidisciplinary teams. • New patients will be seen in clinics at CUH. Diagnostic results and management advice will then be communicated to the patient and their local medical team. Most patients will not then require review at CUH but will require remote contact with the specialist dietician. The service will maintain contact with local specialists and GPs to provide advice as required. • Patients receiving specialist therapies including leptin and IGF1 will be reviewed on a regular basis (up to quarterly) as indicated by their clinical progress. • When required patients will be admitted to CUH for short stays of between five to ten days for initiation of specialist therapies such as rhIGF1, leptin, or multimodal immunosuppression.
Specialist therapies	• Dietary modification is an essential element in the management of patients with these disorders. Specialist input is required to adjust dietary advice for the unusual body composition associated with LD and the need for strict calorie restriction in patients with apparently normal BMIs. • Specialist nursing input, including education of local carers, will be required to support the initiation and on-going use of U500 insulin which will be required in many of the patients. This will involve extensive liaison with and education of GPs, community specialist nurses, and other relevant carers. This specification covers the initiation of U500 therapy and funding is provided for the first 3-months of therapy. Past 3 months funding responsibility for patients responding appropriately to U500 therapy will pass to the patient's responsible CCG or other responsible commissioner. • Recombinant leptin is specifically indicated for patients with severe LD and low leptin levels (<10 µg/L). The national service will select and treat patients with leptin as is clinically

	indicated. The cost of leptin is expressly excluded from the funding for this service.
Abbreviations: BMI, body mass index; CCG, Clinical Commissioning Group; CUH, Cambridge University Hospitals; GP, General Practitioner; IGF, insulin-like growth factor; LD, lipodystrophy; NHS, National Health Service; rh, recombinant human	

Source: NHS England (A03/S(HSS)/b) (8)

8.1.2 International expert guidelines

8.1.2.1 Diagnosis

As LD is ultra-rare disease, awareness is very low and many clinicians are unfamiliar with diagnosis, leading to many patients being undiagnosed or diagnosed late in the course of their disease, when the physical impact is greater and multi-organ damage may be irreversible.(2, 19)

Firm diagnostic criteria have not been established for LD,(2) owing, in part, to difficulty in diagnosing the disease and distinguishing between sub-types. The American Association of Clinical Endocrinologists (AACE) and a 17 member committee of nominees from worldwide endocrine societies have both attempted to develop consensus recommendations for the detection of LD.(2, 19)

Difficulties in diagnosis are recognised as multifactorial. Firstly, recognising the loss of subcutaneous fat is particularly challenging in PL and especially in men in whom low body fat overlaps with normal variation.(2) Secondly, serum leptin levels alone cannot establish or rule out a diagnosis of LD.(2) Serum leptin assays are not standardised and leptin concentrations in patients with LD (especially partial forms) overlap the general population, leptin levels do not help in diagnosis but may help with the choice of therapies.(2) Thirdly, in both congenital and acquired LD, the loss of subcutaneous adipose tissue may be gradual, delaying diagnosis. Finally, when due to the heterogeneity of gene loci involvement in CGL and CPL, genotyping cannot be conclusive.(2)

The suggested diagnostic approach has been proposed by a multi-society practice guideline on the diagnosis and management of LD syndromes, which was published in 2016.(2) In this, Brown et al. recommend that diagnosis initially be based on history, physical examination, body composition and metabolic status.(2) Confirmatory genetic testing is helpful in suspected familial LD and should also be considered in at-risk family members.(2)

Differentiation of genetic and acquired LD can be hampered by the heterogeneity of subcutaneous adipose tissue loss between LD types. With CGL, patients typically have a lack of subcutaneous adipose tissue from infancy, whereas adipose tissue may appear as normal in infancy in patients with AGL.(2) The presence of autoimmune disease increases the suspicion of an acquired subtype.(2)

In patients where there is a suspicion of LD, Brown et al. recommend screening for comorbidities associated with the disease including diabetes, dyslipidaemia, NAFLD and cardiovascular and reproductive dysfunction.(2)

AACE have conducted a MEDLINE literature search and panel discussion to try and reach consensus recommendations for LD diagnosis. Their published findings contain similar suggestions as those published by Brown et al. with clinical characteristics and comorbid conditions being the basis for referral to specialist LD centre.(19)

8.1.2.2 Management

The consensus statement from the AACE on the clinical approach to the detection of LD also includes a section on potential management modalities.(19) The AACE suggest diet and exercise as options for the metabolic management of LD alongside conventional antihyperglycaemic and lipid lowering medications. Metformin, sulfonylureas, thiazolidinediones, and insulin can be used to manage hyperglycaemia, while fibrates and statins can be used to manage hypertriglyceridaemia. They acknowledge, however, that when the complications associated with LD are severe, conventional treatments, alone or in combination, are likely to be inadequate at establishing metabolic control.

The multi-society practice guideline on the diagnosis and management of LD syndromes by Brown et al. recommends diet for managing the metabolic complications of LD - however they note that studies of specific diets in LD are lacking, and recommendations rely on sparse literature and clinical experience.(2) In addition, patients should be encouraged to exercise, however strenuous exercise should be avoided in patients with cardiomyopathy and contact sports should be avoided in patients with severe hepatosplenomegaly and CGL patients with lytic bone lesions.

The guideline recognises that metreleptin is the only drug specifically for the treatment of LD. Metreleptin (with diet) is recommended for GL, as a first-line treatment for metabolic and endocrine abnormalities and may be considered for prevention of these comorbidities in children. In addition, metreleptin may be considered for hypoleptinaemic (leptin <4 ng/mL) patients with PL and severe metabolic derangements (HbA1c >8% and/or triglycerides >500 mg/dL).

The recommended additional treatments for the specific co-morbidities are outlined in Table B10. For dyslipidaemia, it was noted that statins and fibrates should be used with caution due to the increased risk of myopathy, especially in the presence of known myositis or muscular dystrophy. In addition, because cardiovascular risk may be enhanced in lipodystrophic syndromes independent of other risk factors, clinicians may consider applying stricter lipid targets (e.g. low density lipoprotein cholesterol [LDL-C] <100 mg/dL, non-high density lipoprotein cholesterol [non-HDL-C] <130 mg/dL, triglycerides <200 mg/dL), even in patients without diabetes. Furthermore, no treatments have been studied in liver disease linked to LD.

Table B10: Treatments for conditions arising in patients with LD

Co-morbid condition arising as a result of LD	Management
Diabetes	Metformin is a first-line agent for diabetes and insulin resistance. Insulin is effective for hyperglycaemia. In some patients, concentrated preparations and high-doses may be required. Thiazolidinediones may improve metabolic complications in PL but should only be used with caution in GL.
Dyslipidaemia	Statins should be used concomitantly with lifestyle modification (after consideration of age, reproductive status, and tolerance). Fibrates and/or long-chain omega-3 fatty acids should be used for triglycerides >500 mg/dL and may be considered for triglycerides >200 mg/dL.
Hypertension	Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first-line treatments for hypertension in patients with diabetes.
Liver disease	In NAFLD not associated with LD, diet and exercise are first-line treatments, and among pharmacological treatments, vitamin E (in children and adults) and pioglitazone (in adults) have shown the most consistent benefit for liver histopathology. However, these treatments have not been studied in patients with LD and are not approved for NAFLD.
Cosmetic treatment	Patients should be assessed for distress related to LD and referred as necessary to mental health professionals and/or plastic surgeons.
Abbreviations: GL, generalised lipodystrophy; LD, lipodystrophy; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; PL, partial lipodystrophy	

Source: Brown, 2016 (2)

8.2 Describe the clinical pathway of care that includes the proposed use of the technology.

Due to the rarity of LD, many clinicians are unfamiliar with diagnosis and management, and diagnosis can take many years. The majority of new cases of LD in England are identified by diabetes specialists, endocrinologists, lipid specialists or occasionally dermatologists and oncologists. Patients may be referred onto the only specialist centre in the UK (at Addenbrooke's) for baseline assessment, confirmation of diagnosis by clinical examination, with genetic testing where needed and for advice on ongoing management, and on genetic testing for family members where indicated. Treatment with metreleptin in England is currently provided at this centre through the EAP.

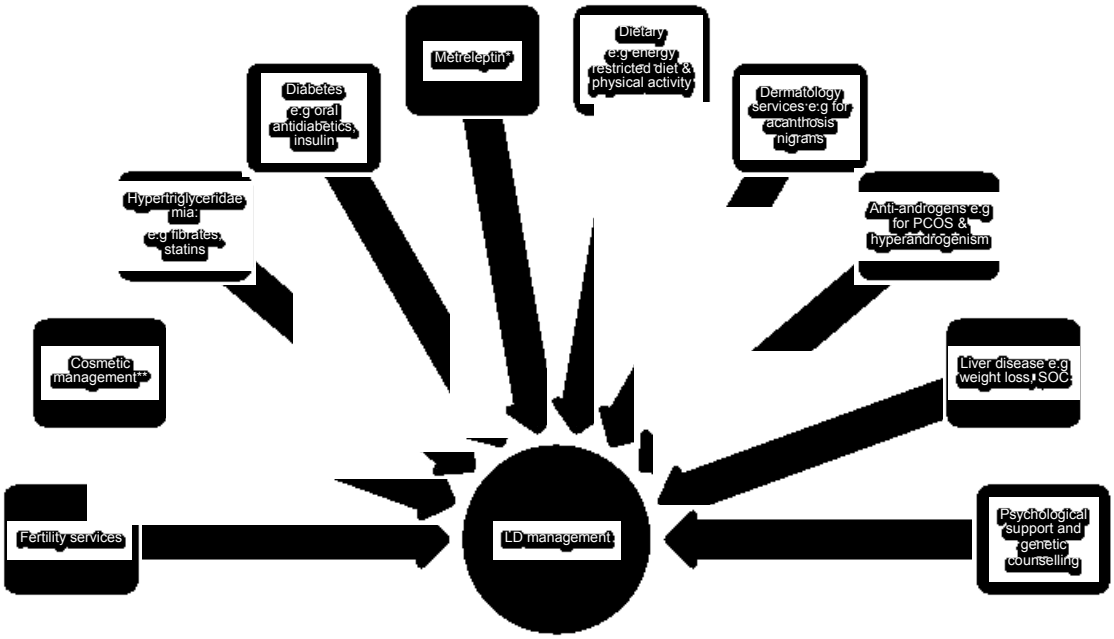
Clinical experts in England stated that they review their patients with LD in the clinic depending on individual needs but usually on a 6-12 monthly basis and usually 6-monthly when the patient is prescribed metreleptin. This is in line with the service specification (Section 8.1.1). Patients are usually reviewed by their local team and/or GP in between appointments at the specialist centre.

There is no standard clinical pathway for the treatment of LD in England. Management of patients with LD is complex (

Figure B11), and overall, gold standard management of LD requires a multidisciplinary team including ideally diabetologists/endocrinologists, dieticians, specialist nurses, and if required specialists in psychological support and genetic counselling. Paediatric patients are discussed at a combined multidisciplinary meeting. Individualised decision-making is needed with close consultation among the patient, physicians, family members, and other carers.

Initially, the standard of care is an energy-restricted diet to lower triglycerides and glucose, but dietary restriction may be challenging to achieve in some patients due to hyperphagia associated with leptin deficiency. Further to dietary management, drug treatments are aimed at treating complications such as diabetes (oral antidiabetic drugs including oral medications such as metformin, and injectable therapies including GLP-1 agonists in some patients and/or insulin) and hypertriglyceridaemia (fibrates, statins), although these may have limited efficacy in some patients. Cosmetic treatment may be required to improve physical appearance, however patients in England may have problems with gaining funding for cosmetic procedures through the NHS and they may need to seek private treatment.(39) Presently there are no effective therapies approved to treat hepatic steatosis or NASH but weight loss can be effective. Anti-androgens may be required for PCOS and hyperandrogenism.(39) Other services that may be required include referral to a dermatologist for severe acanthosis nigricans and/or skin tags and referral to fertility services.(39) As described, metreleptin is available at Addenbrooke's via the EAP, and is the only treatment for patients with LD that can address the underlying cause of the condition. It fulfils an unmet need for patients who are not effectively controlled on standard therapy.

Figure B11: Multifaceted approach to managing LD



Abbreviations: LD, lipodystrophy; PCOS, polycystic ovary syndrome; SOC, standard of care
* Metreleptin is given via the EAP in England
** Cosmetic treatment may not be available on the NHS
At Addenbrooke's there is a separate paediatric clinic that adjoins the adult clinic and is staffed by a consultant paediatrician and paediatric nurse. Paediatric patients are discussed at a combined multidisciplinary meeting.(39)

Source: Stears and Hames, 2014 (39); Brown, 2016 (2)

8.3 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

Apart from metreleptin, there are no other current treatment options available to treat the underlying cause of GL and PL, i.e., leptin deficiency. The other available treatment options only treat about a third of the total disease burden, have a small

effect, and fail to stop disease progression. For example, for patients with LD and associated diabetes and/or hypertriglyceridaemia, current therapies include diet modifications and oral anti-hyperglycaemic agents; however as the disease progresses and more severe conditions manifest, patients often do not respond to treatment.

Studies have reported the high disease burden in LD patients despite being on conventional therapies.(9, 10, 16, 32, 33, 35) For example, in the pivotal study NIH 991265/20010769 the baseline HbA1c was high (mean: 8.6% and 8.8% in the GL and PL subgroup patient groups, respectively), despite 80.3% of GL and 96.8% of PL subgroup patients being on anti-diabetic medications. Similarly, patients had high baseline fasting triglyceride levels (14.7 mmol/L and 15.7 mmol/L in Gl and PL subgroup patients, respectively) despite lipid-lowering medications being used by 51.5% of GL patients and 83.9% of PL subgroup patients. The majority of GL and PL subgroup patients had hypertriglyceridaemia (71% and 94%, respectively) and diabetes mellitus (70% and 84%). Other relevant medical history at baseline in GL patients included hepatomegaly/ hepatosplenomegaly (62%), NASH/steatohepatitis (52%), proteinuria (45%), pancreatitis (27%), and hepatic steatosis (24%), and in the PL subgroup patients had hepatic steatosis and pancreatitis (39% for each) and NASH or steatohepatitis (26%).

This failing response to treatment is a consequence of the underlying absence of leptin and subcutaneous adipose tissue. In many patients with LD, treatment with insulin becomes ineffective due to severe insulin resistance and patients may have difficulty injecting insulin due to the loss of subcutaneous fat in the abdomen or thighs.(21) The long-term benefits of insulin sensitisers such as metformin, remains unclear,(17) meaning that even when the co-morbid condition arising from LD is identified, its treatment is difficult.

In some cases, no treatments are available for the conditions that arise from LD. Presently there are no effective therapies approved to treat hepatic steatosis or NASH and there are limited options for patients with PCOS.(17) Additionally, conventional therapies have no effect on the insatiable hunger and the hyperphagia, making it difficult to maintain an adequate diet and adding to the problem of ectopic fat distribution in the liver and/or muscle.(19)

There is an unmet need for a treatment option that treats the underlying cause of GL and PL as conventional treatments fail in the majority of patients and increase their risk of end organ damage.(5) By correcting the pathophysiology of LD, the metabolic disorders that arise can be addressed, reducing the burden on patients. As the conditions that arise from LD are many and varied, each case is unique in its course,(17, 22) and there is difficulty in understanding how a disease might progress and what treatment options may be required. A treatment option that addresses the underlying pathophysiology of GL and PL will therefore limit this uncertainty, by reducing the development of all consequential conditions.

8.4 Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.

In patients with GL metabolic complications are frequent and are generally severe.(2) Metreleptin is expected to be indicated in patients with congenital or acquired GL, in adults and children (the age threshold is still to be determined by the CHMP). The degree of metabolic complications in patients with PL can be varied, with some patients being treated adequately with lifestyle changes and use of available antidiabetic and lipid-lowering treatments, while others have significant morbidity and mortality resembling that of GL requiring a more mechanistically-based therapy aimed at the underlying leptin deficiency. Based on this, the expected indication for metreleption is in a subgroup of patients with PL who have clinically similar metabolic disturbances as patients with GL and who could equally benefit from metreleptin treatment (the final criteria are yet to be defined by the CHMP).

The care of LD patients in England is expected to remain largely unchanged, with metreleptin continuing to be given to patients at Addenbrooke's, where metreleptin will be prescribed within its marketing authorisation to patients with a clinical need. It is anticipated that metreleptin will be used on top of established clinical management as per the current clinical practice at Addenbrooke’s.

8.5 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a ‘step-change’ in the management of the condition.

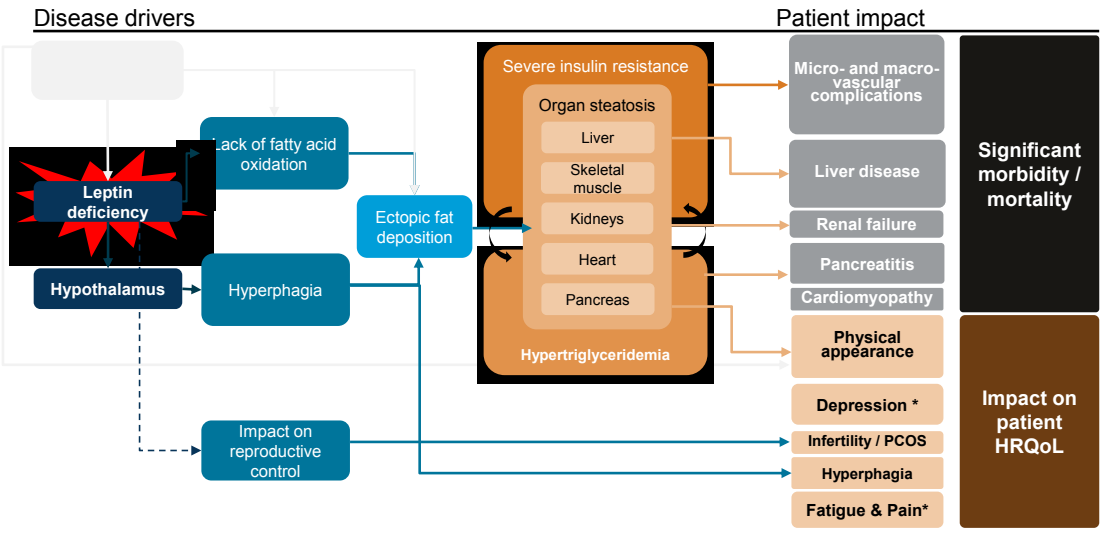
Currently, metreleptin is the only therapy specifically for LD, and therefore represents an important step-change in the management of LD. As described in Section 6, LD is associated with considerable morbidity, mortality and reduced QoL. The major therapeutic approaches in patients with LD are those used in the related metabolic disorder, and include diet, insulin, and oral anti-diabetic and lipid lowering agents. The major problem with this approach is that the metabolic disturbance is severe and does not respond well to these conventional approaches.(63)

In contrast, metreleptin acts on an underlying cause of GL and PL complications, i.e. leptin deficiency. Metreleptin therapy leads to an improvement in hypertriglyceridaemia, insulin resistance, and hyperglycaemia by the following proposed mechanisms (

Figure B12) (31)

- Improving insulin suppression of glucose production in the liver and increasing insulin-stimulated peripheral glucose uptake in the muscle;
- Stimulating fatty acid oxidation throughout the body and lowering plasma, hepatic, and myocellular lipid levels resulting in increased insulin sensitivity;
- Correcting hyperphagia secondary to total or relative leptin deficiency with concomitant reduction in caloric and fat intake.

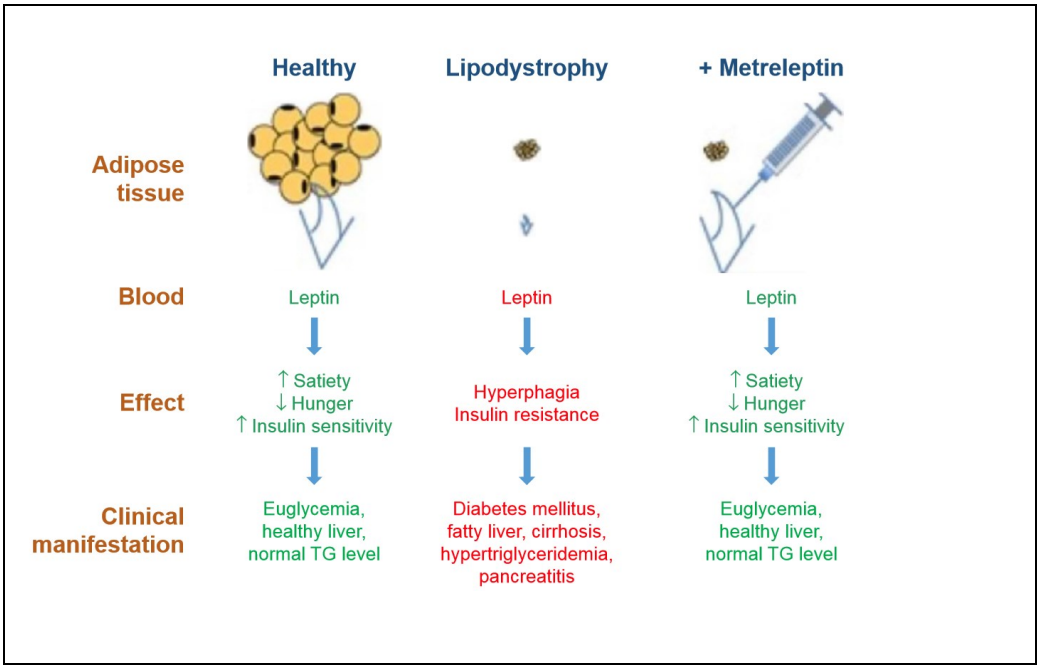
Figure B12. Metreleptin acts on the underlying cause of lipodystrophy (leptin deficiency) which leads to improvement in hypertriglyceridaemia, insulin resistance, and hyperglycaemia



Abbreviations: HRQoL, health-related quality of life; PCOS, polycystic ovary syndrome
Source: Aegerion, created from expert input and the literature

Therefore, leptin acts via multiple mechanisms to decrease triglyceride and other lipid intermediates in LD patients, reducing their accumulation in tissues such as liver and muscle, and ameliorating severe insulin resistance, thereby improving hyperglycaemia and hypertriglyceridaemia (Figure B13).(14, 43, 64, 65)

Figure B13. Clinical action of metreleptin treatment in LD patients



Abbreviations: TG, triglycerides Source: Rodriguez, 2015 (5)

Metreleptin is associated with significant benefits over the current standard of care for which treatment in ineffective or there are no treatment options available: it is effective in controlling metabolic parameters (HbA1c and triglycerides) that have not responded to conventional therapy;(9, 10, 56, 61, 66) it can significantly improve hepatic steatosis and NASH;(57, 58, 64) it is associated with significant improvements in measures of satiety and decreases in food intake;(54, 55) it has been shown to halt or in some cases reverse organ damage associated with LD; female patients experiencing infertility and other reproductive dysfunction (e.g., PCOS) have experienced improvement and successful pregnancy following initiation of metreleptin; and improvements in the physical appearance of LD patients have also been reported.(56, 61, 62)

Overall, metreleptin represents an important step-change in the management of LD patients (GL patients and the subgroup of PL patients), which is providing a single therapy able to control metabolic abnormalities that are not effectively controlled through conventional approaches.(5) In this way, metreleptin is anticipated to reduce the clinical and QoL impact, as well as the cost to the NHS and PSS, associated with the high disease burden currently experienced by patients on standard of care.

8.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

It is not expected that there will be changes to the way current services are organised or delivered as a result of the introduction of metreleptin on the NHS in England. It is anticipated that patients will still be referred to Addenbrooke's, the CUH facility for delivery of the specialised service. There is a chance that approval of metreleptin will help to raise awareness of this little-known disease – this may result in more patients being referred to Addenbrooke's (within the context of a rare disease). These additional patients would not all expected to be suitable candidates for treatment with metreleptin, but they may nonetheless benefit from the expert management at Addenbrooke's with interventions like correct diet having a significant favourable impact.

8.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests will be needed for selecting or monitoring patients over and above currently existing technologies. Testing for HbA1c and triglycerides are routine in the management of LD and tests for leptin are also available at Addenbrooke's. In the NHS service specification (Section 8.1.1) metreleptin is specifically indicated for patients with severe LD and low leptin levels (<10 μg/L) and the national service selects and treats patients with leptin as is clinically indicated.(8) Therefore, the resources are already available to identify the patients. (8) Therefore, the resources are already available to identify the patients. Potential implementation of commercial/post-marketing neutralising antibody testing in the EU, possibly in patients with severe or serious infections, is being discussed with the CHMP, but is currently unresolved.

Metreleptin is administered as a subcutaneous injection by the patient or carer. Healthcare professionals should provide patients and carers with training on the reconstitution of the product and proper subcutaneous injection technique, so as to avoid intramuscular injection in patients with minimal subcutaneous adipose tissue.

Patients and/or carers should prepare and administer the first dose of the medicinal product under the supervision of a qualified healthcare professional. A review of the patient's self-administration technique is recommended every six months whilst taking metreleptin.

8.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

No additional facilities, technologies or infrastructure will be required.

8.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

There are no tests, investigations, facilities or technologies that would no longer be needed.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

9.1 Identification of studies

Published studies

9.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

A SLR was carried out to search for trials of metreleptin and trials of relevant comparators. The objective of the SLR was to: systematically search and review all available evidence on the clinical effectiveness (including the impact on clinical and metabolic outcomes) associated with metreleptin as an adjunct to diet as a replacement therapy and relevant comparators for the treatment of LD. Metreleptin is the first treatment specifically designed to treat the LD itself; as such the relevant comparator is standard of care. The search strategy, which was conducted in line with the documented expected needs of international health technology assessment (HTA) submission templates including NICE, is detailed in Appendix Section 17.1. Electronic databases were searched to identify relevant published studies, including Ovid MEDLINE and MEDLINE In-Process; Ovid EMBASE; Database of Abstracts and Review of Effects; The Cochrane Library, including the Cochrane Database of Systematic Reviews and the HTA Database; NHS Economic Evaluation Database; and the grey literature, as described in Appendix Section 17.1.1 and 17.1.5.

Unpublished studies

9.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Sources of unpublished data relevant to the NICE scope were provided by Aegerion, and were assessed according to the same methods as described for the published sources (please see Section 9.1.1 and Section 17.1).

9.2 Study selection

Published studies

9.2.1 Complete table to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C11 describes the inclusion and exclusion criteria (PICOS) used to select studies from the published literature and unpublished studies.

Table C11: Selection criteria used for published and unpublished studies

Inclusion Criteria	
Population	Patients with congenital or acquired GL, in adults and children 2 years of age and above Patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA1c ≥6.5 %, in adults and children 2 years of age and above Patients with rare LD syndromes (e.g. Donohue syndrome, mandibuloacral dysplasia (type A and type B) and Wiedemann Rautenstrauch syndrome), in adults and children 2 years of age and above
Interventions	Studies considering an interventional treatment
Outcomes	Clinical outcomes, including (not limited to): distribution of fat (% fat loss across face and neck, abdomen, thorax, upper limbs and lower limbs and number of fat sparing across face and neck abdomen, upper limb, lower limb, palms and soles), menstrual irregularities (polycystic ovaries etc.), hirsutism, growth, treatment related adverse events and mortality associated with LD and comorbidities associated with underlying disease Metabolic outcomes, including (not limited to): blood glucose (fasting glucose mg/dl), serum insulin (insulin (uIU/ml), HbA1c %, lipid profile (triglycerides mg/dl, total cholesterol mg/dl, HDL-C mg/dl and LDL-C mg/dl), liver function tests (AST U/L, ALT U/L), alkaline phosphatase (U/L), blood urea nitrogen (mg/dl), creatinine (mg/dl) and leptin (ng/ml) Metabolic complications, including (not limited to): diabetes, hypertriglyceridemia, insulin resistance and acute pancreatitis Quality of life outcomes if measured within the trial, including standardised and non-standardised outcomes

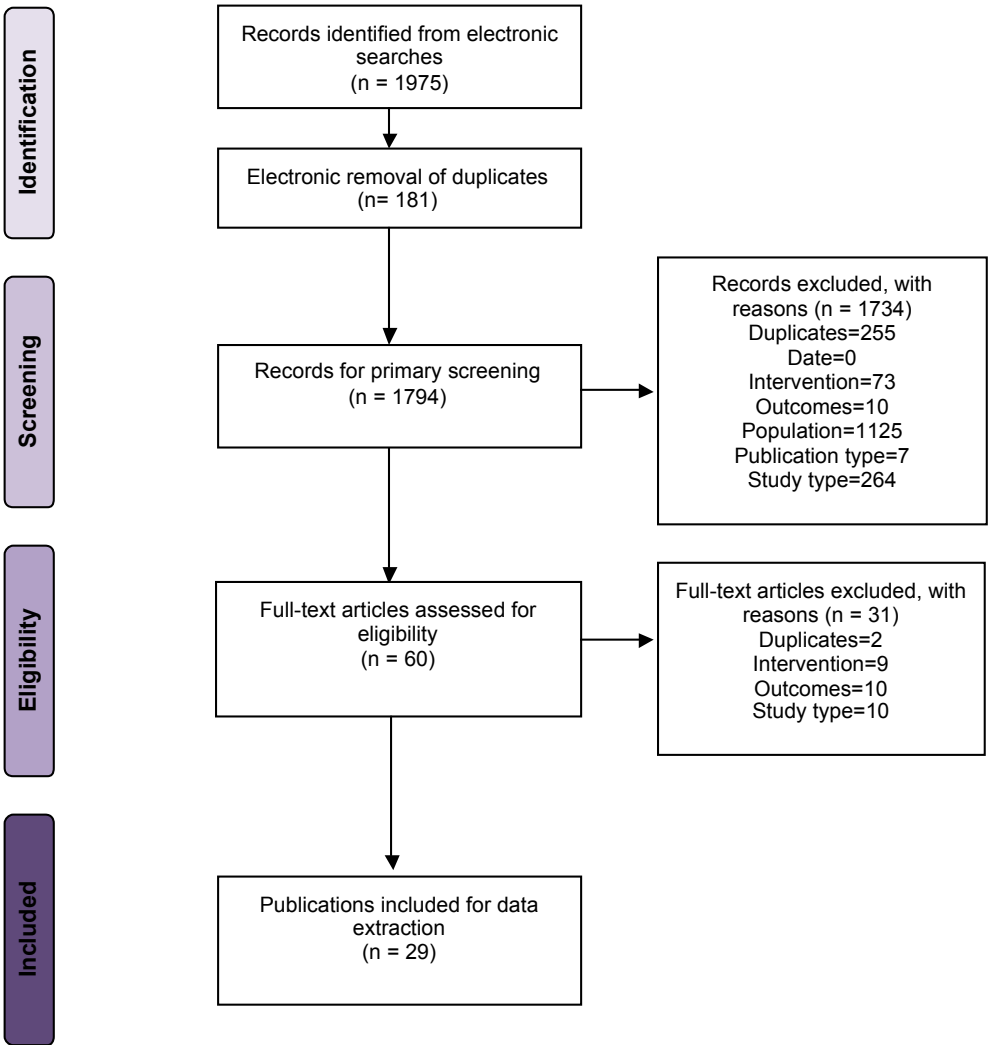
Study design	RCTs, non-RCTs (e.g. single arm trials, real world/observational studies), pooled analyses, retrospective analyses, long-term extension phase studies, systematic reviews/meta-analyses Ongoing clinical studies and unpublished reports available internally at Aegerion Pharmaceuticals (unpublished)
Language restrictions	None
Search dates	Journal articles, reports and summaries: No restrictions Conference abstracts published within the last four years (January 2013-January 2017, inclusive)
Exclusion Criteria	
Population	HIV-associated LD LD secondary to drug administration (insulin growth hormone, steroids, antibiotics and vaccinations) LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections LD in children <2 years of age
Interventions	Studies considering a non-interventional treatment
Outcomes	Studies reporting symptoms or short-term outcomes only Key search terms including: anatomy, histology, diagnosis, genetics, preclinical and reaction time
Study design	Phase 1 RCTs Study protocols Abstract with more recent existing full text publication Abstract or paper with insufficient reporting on population, study type or outcomes Healthy volunteer studies Animal studies Editorials/letters General reviews (other than systematic reviews)
Language restrictions	-
Search dates	Conference abstracts published before 2013
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; HIV,Human immunodeficiency virus; LD, lipodystrophy; LDL-C, low density lipoprotein cholesterol; RCT, randomised controlled trial	

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The electronic database searches initially identified 1975 articles, of which 1794 were screened after the removal of duplicates (Figure C14). After the initial screening, a total of 60 articles were retrieved for full-text assessment, of which 29 met the eligibility criteria. No additional publications were identified from searches of key international HTA websites or the grey literature. Overall, 26 publications reported on outcomes from single-arm trials evaluating metreleptin, one publication reported on a

study evaluating individualised diets with oral zinc supplementation and two publications reported on a SLR and meta-analysis of metreleptin studies.

Figure C14: **PRISMA flow diagram for the identification of studies reporting on the efficacy and safety of metreleptin and comparators**



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Please see Section 9.2.1, which describes the inclusion/exclusion criteria for both published and unpublished evidence.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Aegerion provided CSRs for the studies NIH 991265/20010769 and FHA101.

9.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C11 and C12.

No randomised controlled trials (RCTs) were identified in the search.

Two relevant single-arm studies were identified in the SLR (Table C12).

NIH 991265/20010769 (NCT00025883). This was an open-label, single-arm study conducted at the NIH in the US. This study had been ongoing at the NIH from 2000-2014, with continuous enrolment and variable duration of follow-up. The primary source of evidence is the CSR provided by Aegerion Pharmaceuticals; this current CSR is based on all available data from the final integrated analysis on all patients (N=107) over the 14-year development period of metreleptin.(9) A number of publications related to this study were identified which were published while the study was ongoing and thus report on fewer patients than in the CSR.

FHA101 (NCT00677313). This was an open-label expanded access study designed to provide metreleptin under a treatment IND protocol for the treatment of patients with diabetes mellitus and/or hypertriglyceridaemia associated with LD. The primary source of evidence is the CSR provided by Aegerion, which is based on the final integrated data on all patients from this study;(10) as with study NIH 991265/ 20010769 as of December 2014, all patients were either off metreleptin treatment or had transitioned to commercial product or free-drug programmes.

Table C12: List of relevant studies

Study name (acronym)	Primary study reference	Other references identified	Population	Intervention
NIH 991265/20010796 (NCT00025883)	CSR(9)	Diker-Cohen et al. 2015(66) Christensen et al. 2014(67) Joseph et al. 2014(68) Safar Zadeh et al. 2013(58) Muniyappa et al. 2013(69) Brown et al. 2013(70) Chan et al. 2011(71) Park et al. 2007(72) Oral, et al. 2006(73) Javor et al. 2005a(14)	Patients with GL or PL	Metreleptin

Study name (acronym)	Primary study reference	Other references identified	Population	Intervention
		Javor et al. 2005b(57) Musso, et al. 2005(60) Moran, et al. 2004(55) Petersen et al. 2002(74) Oral et al. 2002(75)		
FHA101 (NCT00677313)	CSR(10)	Ajluni et al. 2016(61)	Patients with GL or PL	Metreleptin
Abbreviations: CSR, clinical study report; GL, generalised lipodystrophy; PL, partial lipodystrophy				

9.3.2 State the rationale behind excluding any of the published studies listed in tables C13 and C14.

The following publications were excluded (Table C13). These studies were not included in the EMA (or the FDA) application; they only include a small number of patients and/or a population not relevant to this submission e.g. Japanese patients and/or PL patients who are not specific to the sought after indicated population.

Table C13: Excluded published studies

Primary study reference	**Study name (acronym)**	**Population**	**Intervention**
Beltrand et al. 2007 (76) Full publication	_	Children with BSCL (N=7)	Metreleptin
Beltrand, et al. 2010 (77) Full publication	_	Children with BSCL (N=8)	Metreleptin
Simha, et al. 2012 (78) Full publication	NCT00457938	FPLD2 patients (N=24)	Metreleptin
Asthana, et al. 2015 (79) Abstract	_	GL (N=9) or PL (N=8) (N=17)	Metreleptin
Brown, et al. 2015 (80) Abstract	_	Previously leptin-treated (N=5, all GL, treatment duration 1-12 years) and leptin-naïve (N=10, 9 PL) subjects (N=15)	Metreleptin
Ebihara, et al. 2007 (81) Full publication	_	GL patients (Japanese) (N=7)	Metreleptin
Schlogl, et al. 2016 (82) Full publication	_	Patients with GL or PL (N=9)	Metreleptin
Vatier, et al 2016 (83)	EAP	Patients with GL or PL (N=16)	Metreleptin
Araujo-Vilar, et al. 2015 (56)	EAP	Patients with GL or PL (N=9)	Metreleptin
Abbreviations: BSCL, Berardinelli-Seip congenital lipodystrophy; EAP, Early Access Programme; FPLD2, familial partial lipodystrophy, Dunnigan variety; GL, generalised lipodystrophy; PL, partial lipodystrophy			

9.4 Summary of methodology of relevant studies

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C15 and C16 as appropriate. A separate table should be completed for each study

9.4.1.1 Study NIH 991265/20010769

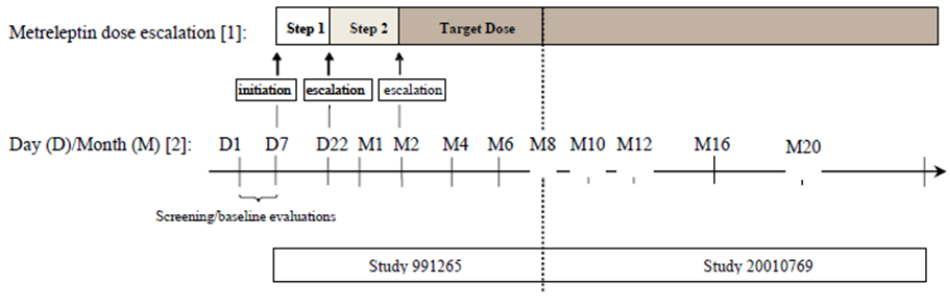
Study NIH 991265/20010769 was an open-label, investigator-sponsored trial conducted at the NIH to examine whether treatment with metreleptin could improve the metabolic sequelae, including pathological derangements in glucose and lipid homeostasis, found in patients with LD syndromes.(66, 75, 84) Patients were enrolled from the US, countries in Europe including the UK, and other countries.(9)

Study NIH 991265 was a pilot, dose-escalation study to determine the safety and efficacy of short-term leptin replacement (up to 8 months) and NIH 20010769 was conducted to determine the long-term safety and efficacy of metreleptin treatment for patients with LD.(66, 75, 84) Study NIH 20010769 allowed for the rollover of patients from the pilot study, as well as for direct enrolment of new patients. Although conducted as separate studies, NIH 991265 and NIH 20010769 can be considered as a single extended study since the two studies employed a similar protocol and all but one of the patients studied under the pilot study continued long-term treatment in the second study. The study was conducted in the US where metreleptin was approved by the FDA in 2014. As of December 2014, all patients were either off metreleptin treatment or had transitioned to commercial product or free-drug programmes.(9)

Figure C15 presents the study design and the visit structure for patients enrolled in study NIH 991265 and 20010769. Patients on the pilot study who elected to continue metreleptin treatment were transferred to the long-term study at ~Month 8 of treatment.

Figure C15: Study design for studies (a) NIH 991265 and (b) NIH 20010769

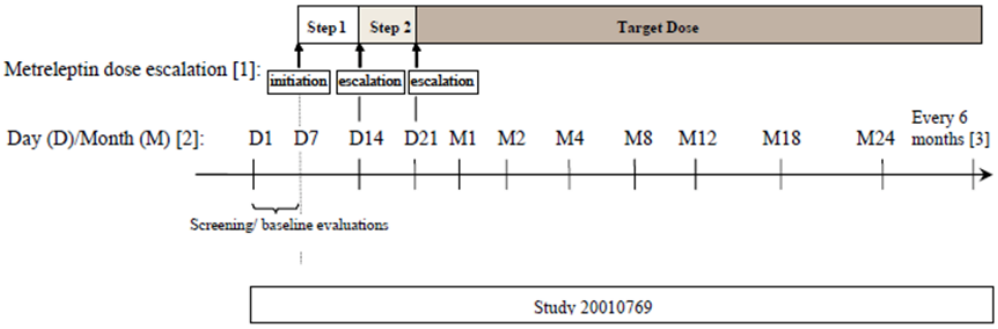
(a)



[1] Metreleptin target dose for each patient was achieved via a 2-step dose escalation.

[2] Following the first dose on Day 7, patients were observed as inpatients for at least 48 hours. Patients were not required to visit the site on Day 22.

(b)



[1] Metreleptin target dose for each patient was initially achieved via a 2-step dose escalation. As knowledge was gained, patients who initiated later started at higher doses and required minimal to no dose escalation.

[2] Following the first dose on Day 7, patients were observed as inpatients for at least 48 hours. Patients were not required to visit the site on Day 14 or Day 21.

Source: Study NIH 991265/20010769 CS R(9)

Patients received self-administered (by the patient or caregiver) subcutaneously metreleptin injections in one to two daily doses ranging from 0.06 to 0.24 mg/kg/day in study NIH 20010769 (0.01 to 0.08 mg/kg/day in study NIH 991265). Starting doses were dependent on age and gender, and doses were adjusted to achieve metabolic control and avoid excessive weight loss. Anti-hyperglycaemic and lipid-lowering regimens were modified if clinically indicated.

The co-primary efficacy endpoints in this study were: actual change from baseline in HbA1c at Month 12, and percent change from baseline in fasting serum triglycerides at Month 12.

A summary of the methodology is shown in

Table C14.

Table C14: Summary of methodology for study NIH 991265/20010769

Study name	NIH 991265/20010769
Objective	To evaluate the safety and efficacy of recombinant methionyl human leptin (metreleptin) replacement in patients with GL and PL
Location	The studies were conducted at the NIH, however patients were also enrolled from countries outside the US: GL: 59% were from the US; 20% from Europe/Eastern Mediterranean (Belgium, UK, Germany, Italy, Lithuania, Spain, Turkey, Albania, Israel, and Serbia); 18% from other countries.* PL: 78% from the US, 7% from Europe/Eastern Mediterranean; 15% from other countries*

Design	Open-label, single-arm
Duration of study	Continuous enrolment over 14 years (2000-2014): NIH 991265: 8 months NIH 20010769: Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months
Patient population	Patients with GL or PL
Sample size	N=107 (GL=66; PL=41; PL subgroup[a]=31)*
Inclusion criteria	Age: Study NIH 2001769: 6 months; Study NIH 991265: >5 years Clinically significant LD identified as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient Circulating leptin levels: Study NIH 2001769: <12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years; Study NIH 991265: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males Presence of at least 1 of the following metabolic abnormalities: • Presence of diabetes mellitus • Fasting insulin concentration >30 µU/mL (208.4 pmol/L) • Fasting triglyceride concentration >200 mg/dL (>2.26 mmol/L), or postprandially elevated triglyceride concentration[a] Triglyceride concentration >500 mg/dL (>5.65 mmol/L) when fasting is not clinically indicated (e.g., infants)[b]
Exclusion criteria	General: Pregnant women, women in their reproductive years who did not use an effective method of birth control, and women who were nursing or who were lactating within 6 weeks of having completed nursing. Exclusions for underlying disease likely to increase side effects or to hinder objective data collection: • Known infectious liver disease (in Study NIH 99165, known liver disease due to causes other than NASH) • Known human immunodeficiency (HIV) infection • Current alcohol or substance abuse • Psychiatric disorder impeding competence or compliance • Active tuberculosis • Use of anorexigenic drugs • Other condition(s) that in the opinion of the clinical investigators would impede completion of the study Patients who have a known hypersensitivity to Escherichia coli-derived proteins
Statistical tests*	The primary and key secondary efficacy analyses were performed primarily on the FAS (all patients who received at least 1 dose of study drug and had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit). The primary and key secondary endpoints were summarised using descriptive statistics and 95% CIs. P values for the primary endpoints were computed using paired t-tests to determine if the change from baseline to Month 12 was significantly different from 0, at a one-sided α-level of 0.025. The LOCF method was used to impute any missing Month 12 results. The imputation only took into account results that were at least 6 months (180 days) post-baseline. Thus, the analysis included all patients that had baseline and at least Day 180 measurements. A MMRM analysis was used to assess changes over time for the entire duration of the study.
Primary outcomes	• Actual change from baseline in HbA1c at Month 12 Percent change from baseline in fasting serum triglycerides at Month 12
Key secondary outcomes	Proportion of patients achieving target actual decreases of: • ≥1% decrease in HbA1c or ≥30% decrease in fasting serum triglycerides at Month 12 • ≥1.5% decrease in HbA1c or ≥35% decrease in fasting serum triglycerides at Month 12 • ≥2% decrease in HbA1c or ≥40% decrease in fasting serum triglycerides at Month 12 Actual and percent change from baseline in fasting plasma glucose levels at Month 12

Other relevant secondary outcomes	• Actual change from baseline in HbA1c at each post-baseline visit • Percent and actual change from baseline in fasting serum triglycerides at each postbaseline visit • Actual and percent change from baseline in fasting lipids (total cholesterol, LDL-C, HDL-C) through Month 12 • Actual change from baseline in ALT and AST at each post-baseline visit through Month 12 Actual change from baseline in liver volume at each post-baseline visit through Month 12
Other endpoints of relevance	• Assessment of concomitant medications • Adverse events (including deaths, and cases of pancreatitis and infections) • Growth and pubertal status Liver volume and pathology: Ultrasound of the liver and, if abnormalities are found, possibly liver biopsies
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI,confidence interval; FAS, full analysis set; FFA, free fatty acid; GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; HIV, human immunodeficiency virus; LD, lipodystrophy; LDL-C, low density lipoprotein cholesterol; LOCF, last observation carried forward; MMRM, Mixed-effect Model Repeated Measures; NASH, non-alcoholic steatohepatitis; NIH, National Institutes of Health; PL, partial lipodystrophy; UK, United Kingdom; US, United States [a] PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L [b] Inclusion criteria for study NIH 20010769 (but not NIH 991265)	

Source: Oral 2002(75); Diker-Cohen 2015 (66); Clinicaltrials.gov NCT00025883 (84); *Study NIH 991265/20010769 CSR (9)

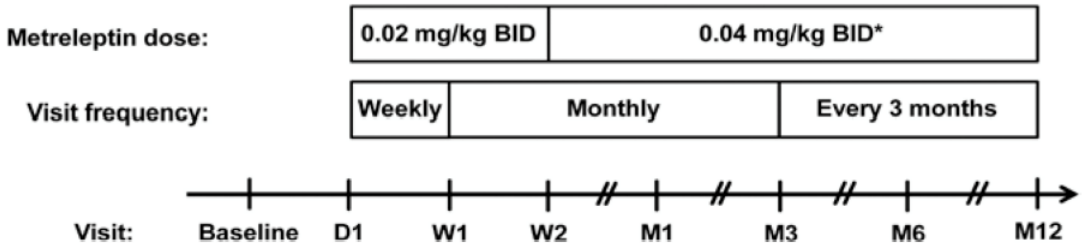
9.4.1.2 Study FHA101

Study FHA101 was an open-label, expanded access study designed to provide metreleptin for the treatment of patients with diabetes mellitus and/or hypertriglyceridaemia associated with LD. The study was initiated in 2008 in the US and as with study NIH991265/ 20010769 as of December 2014, all patients were either off metreleptin treatment or had transitioned to commercial product or free-drug programmes.(10) All patients were enrolled from the US.

On Day 1 and after collection of baseline measurements and training, patients or caregivers injected metreleptin subcutaneously at 0.02 mg/kg twice daily (BID) for one week, modified to one month in June 2009, followed by 0.04 mg/kg BID (Figure C16). Dosage adjustments were allowed based on patient response. Dose titration up to 0.08 mg/kg BID was allowed if there were no improvements in metabolic parameters, and a reduction in target dose was permitted if tolerability became an issue. If metabolic parameters were stabilised after one year of treatment, then a decrease in dosing frequency from BID to once daily was allowed. Patients continued concomitant glucose-and lipid-lowering medications after the baseline visit, and further adjustments were permitted at the discretion of the treating physician.

Patients met with their treating physician one week after the first treatment and monthly for the first 3 months, followed by every 3 months throughout the first year. Following one year of treatment, patient visits were scheduled every 6 months or more frequently as deemed appropriate by the Investigator.

Figure C16: Study design for FHA101



Abbreviations: BID = twice daily; D = day; M = month; W = week.
*Metreleptin dose titration up to 0.08 mg/kg BID was allowed if there were no improvements in metabolic parameters, and a reduction in target dose was permitted if tolerability became an issue.
Source: Ajluni 2016(61)

The co-primary efficacy endpoints in this study were: actual change from baseline in HbA1c at Month 12, and percent change from baseline in fasting serum triglycerides at Month 12.

A summary of the methodology is shown in **Table C15**.

Table C15: Summary of methodology for study FHA101

Study name	NIH 991265/20010769
Objective	To evaluate the safety and efficacy of recombinant methionyl human leptin (metreleptin) replacement in patients with GL and PL
Location	The studies were conducted at the NIH, however patients were also enrolled from countries outside the US: GL: 59% were from the US; 20% from Europe/Eastern Mediterranean (Belgium, UK, Germany, Italy, Lithuania, Spain, Turkey, Albania, Israel, and Serbia); 18% from other countries.* PL: 78% from the US, 7% from Europe/Eastern Mediterranean; 15% from other countries*
Design	Open-label, single-arm
Duration of study	Continuous enrolment over 14 years (2000-2014): NIH 991265: 8 months NIH 20010769: Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months
Patient population	Patients with GL or PL
Sample size	N=107 (GL=66; PL=41; PL subgroupa=31)*
Inclusion criteria	Age: Study NIH 2001769: 6 months; Study NIH 991265: >5 years Clinically significant LD identified as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient Circulating leptin levels: Study NIH 2001769: <12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years; Study NIH 991265: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males Presence of at least 1 of the following metabolic abnormalities: • Presence of diabetes mellitus

	• Fasting insulin concentration >30 µU/mL (208.4 pmol/L) • Fasting triglyceride concentration >200 mg/dL (>2.26 mmol/L), or postprandially elevated triglyceride concentrationa Triglyceride concentration >500 mg/dL (>5.65 mmol/L) when fasting is not clinically indicated (e.g., infants)b
Exclusion criteria	General: Pregnant women, women in their reproductive years who did not use an effective method of birth control, and women who were nursing or who were lactating within 6 weeks of having completed nursing. Exclusions for underlying disease likely to increase side effects or to hinder objective data collection: • Known infectious liver disease (in Study NIH 99165, known liver disease due to causes other than NASH) • Known human immunodeficiency (HIV) infection • Current alcohol or substance abuse • Psychiatric disorder impeding competence or compliance • Active tuberculosis • Use of anorexigenic drugs • Other condition(s) that in the opinion of the clinical investigators would impede completion of the study • Patients who have a known hypersensitivity to Escherichia coli-derived proteins
Statistical tests*	The primary and key secondary efficacy analyses were performed primarily on the FAS (all patients who received at least 1 dose of study drug and had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit). The primary and key secondary endpoints were summarised using descriptive statistics and 95% CIs. P values for the primary endpoints were computed using paired t-tests to determine if the change from baseline to Month 12 was significantly different from 0, at a one-sided α-level of 0.025. The LOCF method was used to impute any missing Month 12 results. The imputation only took into account results that were at least 6 months (180 days) post-baseline. Thus, the analysis included all patients that had baseline and at least Day 180 measurements. A MMRM analysis was used to assess changes over time for the entire duration of the study.
Primary outcomes	• Actual change from baseline in HbA1c at Month 12 • Percent change from baseline in fasting serum triglycerides at Month 12
Key secondary outcomes	Proportion of patients achieving target actual decreases of: • ≥1% decrease in HbA1c or ≥30% decrease in fasting serum triglycerides at Month 12 • ≥1.5% decrease in HbA1c or ≥35% decrease in fasting serum triglycerides at Month 12 • ≥2% decrease in HbA1c or ≥40% decrease in fasting serum triglycerides at Month 12 • Actual and percent change from baseline in fasting plasma glucose levels at Month 12

Other relevant secondary outcomes	• Actual change from baseline in HbA1c at each post-baseline visit • Percent and actual change from baseline in fasting serum triglycerides at each postbaseline visit • Actual and percent change from baseline in fasting lipids (total cholesterol, LDL-C, HDL-C) through Month 12 • Actual change from baseline in ALT and AST at each post-baseline visit through Month 12 • Actual change from baseline in liver volume at each post-baseline visit through Month 12
Other endpoints of relevance	• Assessment of concomitant medications • Adverse events (including deaths, and cases of pancreatitis and infections) • Growth and pubertal status • Liver volume and pathology: Ultrasound of the liver and, if abnormalities are found, possibly liver biopsies
Study name	FHA101
Objective	To provide expanded access to metreleptin to patients with LD and associated metabolic disorders such as diabetes mellitus and/or hypertriglyceridaemia and to test the safety and efficacy of metreleptin in this population of patients.
Location	Six centres in the US*
Design	Open-label, expanded-access
Duration of study	Continuous enrolment over 6 years (2008-2014)*: Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months
Patient population	Patients with GL or PL (including subgroup of PL patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L)
Sample size	N=41 (GL= 9; PL=32; PL subgroup=7)*
Inclusion criteria	Male or female ≥5 years old Physician-confirmed LD as defined by evidence of generalised (whole body) or partial (limbs) loss of body fat outside the range of normal variation Diagnosed with at least 1 of the following 2 metabolic disorders: • Diabetes mellitus • Hypertriglyceridaemia as defined by fasting triglyceride concentrations >2.26 mmol/L (>200 mg/dL)
Exclusion criteria	Diagnosed with human immunodeficiency virus (HIV) infection Clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the Investigator Acquired LD and clinically significant haematologic abnormalities (such as neutropaenia and/or lymphadenopathy) Known infectious liver disease Known allergies to E. coli-derived proteins or hypersensitivity to any component of study treatment
Statistical tests*	The primary and key secondary efficacy analyses were performed primarily on the FAS (all patients who received at least 1 dose of study

	drug and had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit). The primary and key secondary endpoints were summarised using descriptive statistics and 95% CIs. P values for the primary endpoints were computed using paired t-tests to determine if the change from baseline to Month 12 was significantly different from 0, at a one-sided α-level of 0.025. The LOCF method was used to impute any missing Month 12 results. The imputation only took into account results that were at least 6 months (180 days) post-baseline. Thus, analysis of primary efficacy endpoints included all patients that have baseline and at least Month 6 measurements. A MMRM analysis was used to assess changes over time for the entire duration of the study.
Primary outcomes	• Actual change from baseline in HbA1c at Month 12 • Percent change from baseline in fasting serum triglycerides at Month 12
Key secondary outcomes	Proportion of patients achieving target actual decreases of: • ≥1% actual decrease in HbA1c or ≥30% decrease in fasting triglycerides at Month 12 • ≥1.5% decrease in HbA1c or ≥35% decrease in fasting triglycerides at Month 12 • ≥2% actual decrease in HbA1c or ≥40% decrease in fasting triglycerides at Month 12 • Actual and percent change from baseline for fasting glucose levels at Month 12
Other relevant secondary outcomes	• Actual change from baseline in HbA1c at each post-baseline visit • Percent and actual change from baseline in fasting serum triglycerides at each postbaseline visit • Actual change from baseline in ALT and AST at each post-baseline visit through Month 12
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FAS, full analysis set; FFA, free fatty acid; GL,generalised lipodystrophy; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; HIV, human immunodeficiency virus; LD, lipodystrophy; LDL-C, low density lipoprotein cholesterol; LOCF, last observation carried forward; MMRM, Mixed-effect Model Repeated Measures; NASH, non-alcoholic steatohepatitis; NIH, National Institutes of Health; PL, partial lipodystrophy; UK, United Kingdom; US, United States [a] PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L [b] Inclusion criteria for study NIH 20010769 (but not NIH 991265)	

Source: Clinicaltrials.gov NCT00677313(85); Ajluni, 2016 (61); *Study FHA101 CSR (10)

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Table C12 in Section 9.3.1 presents all studies and sources identified in the SLR.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

9.4.3.1 Patient population

Study NIH 991265/20010769 enrolled and treated more patients than FHA101: 107 patients in NIH 991265/20010769 (66 patients had GL and 41 had PL, including 31 patients who were included in the PL subgroup) and 41 in study FHA101 (9 patients had GL and 32 had PL, including 7 patients in the PL subgroup). Although study NIH 991265/20010769 was conducted in the US at the NIH, patients were also enrolled from other countries including in Europe/Eastern Mediterranean countries (see

Table C14). All patients in FHA101 were from the US.

9.4.3.2 Baseline characteristics

Baseline characteristics for studies NIH 991265/20010769 and FHA101 are shown in Table C16 and Table C17, respectively.

Baseline demographics
Among the 66 patients with GL in study NIH 991265/20010769, 77% were female with Caucasians representing 47% of the population; in the PL subgroup, all but 1 of the 31 patients was female and the majority were Caucasian (84%) (**Table C16**). In study FHA101, 8 (89%) of the 9 GL patients and all 7 patients in the PL subgroup were female, and the majority were Caucasian (**Table C17**).

In study NIH 991265/20010769 the median age of the GL group was 15 years with 68% of patients <18 years of age; patients in the PL subgroup were older (median age 38 years) compared with patients in the GL group, with 84% ≥18 years of age.

In study FHA101 most patients in both groups were ≥18 years of age at the time of enrolment.

Baseline metabolic abnormalities
Baseline data for HbA1c, triglycerides, and glucose levels reflect the severity of the metabolic abnormalities observed in patients with LD and clearly show that the PL subgroup selected for evaluation of the effectiveness of metreleptin was similar, if not more compromised, compared to the group of patients with GL (**Table C16** and **Table C17**). These metabolic abnormalities were present despite the high use of antidiabetic medications and lipid-lowering therapies.

In study NIH 991265/20010769 median HbA1c at baseline was 8.7% for patients with GL and 8.6% for patients in the PL subgroup (**Table C16**). The majority of patients met the diagnostic criteria for diabetes mellitus having HbA1c ≥6.5% at baseline, including 74% of GL patients and 94% of patients in the PL subgroup; poor glycaemic control as evidenced by HbA1c ≥8% was noted in 64% and 61% of patients, respectively. The median fasting triglyceride concentration was 4.6 mmol/L

in GL patients and was higher in the PL subgroup with a median of 5.5 mmol/L, indicating the severity of hypertriglyceridaemia in this subgroup of patients.

In general, the baseline metabolic abnormalities for patients in study FHA101, although abnormal, were not as elevated as those for patients in study NIH 991265/20010769 (**Table C17**). Median HbA1c at baseline was 8.4% for the 9 patients with GL and 7.6% for the 7 patients in the PL subgroup, with 67% and 86%, respectively, having HbA1c ≥6.5% at baseline. Median fasting triglyceride concentrations were 3.3 mmol/L in GL patients and 2.9 mmol/L in the PL subgroup, with 6 patients (67%) and 4 patients (57%), respectively, having triglyceride levels ≥2.26 mmol/L, and 3 patients (33%) and 1 patient (14%) having triglyceride levels ≥5.65 mmol/L.

Table C16: Baseline characteristics for study NIH 991265/20010769

Characteristic	GL (N = 66)	PL (N = 41)	
		PL subgroup[a] (N = 31)	Overall (N = 41)
Female, n (%)	51 (77.3)	30 (96.8)	40 (97.6)
Race, n (%)			
Caucasian	31 (47.0)	26 (83.9)	36 (87.8)
Black	16 (24.2)	0	0
Asian/Native American/Hispanic/Other	3 (4.5)/ 2 (3.0)/ 11 (16.7)/ 3 (4.5)	1 (3.2)/ 0 / 2 (6.5)/ 2 (6.5)	1 (2.4)/ 0/ 2 (4.9)/ 2 (4.9)
Age, years, median (range)	15.0 (1.0, 68.0)	38.0 (15.0, 64.0)	34.0 (10.0, 64.0)
<18 years	45 (68.2)	5 (16.1)	8 (19.5)
≥18 years	21 (31.8)	26 (83.9)	33 (80.5)
LD type, n (%)			
Acquired	21 (31.8)	4 (12.9)	6 (14.6)
Congenital/Familial	45 (68.2)	27 (87.1)	35 (85.4)
Fasting leptin, ng/ml, median (range)	1.0 (0.2, 5.3)	5.9 (1.6, 16.9)	5.9 (1.0, 16.9)
BMI, kg/m^2, median (range)	20.5 (14.0, 29.5)	25.1 (18.6, 33.3)	25.3 (17.7, 33.3)
HbA1c, %			
Median (range)	8.7 (4.5, 13.7)	8.6 (5.7, 13.3)	7.8 (4.6, 13.3)
≥6.5, n (%)	49 (74.2)	29 (93.5)	29 (70.7)
≥8.0, n (%)	42 (63.6)	19 (61.3)	19 (46.3)
Fasting plasma glucose, mmol/L, median (range)	10.3 (5.04)	9.9 (4.33)	8.7 (4.35)
Fasting triglycerides, mmol/L			
Median (range)	14.5 (25.29)	14.8 (25.72)	12.0 (22.85)
≥2.26 mmol/L	50 (75.8)	27 (87.1)	34 (82.9)
≥5.65 mmol/L	26 (39.4)	15 (48.4)	15 (36.6)
ALT, >ULN, n (%)	49 (74.2)	9 (29.0)	14 (34.1)
AST, >ULN, n (%)	36 (54.5)	7 (22.6)	10 (24.4)

Anti-diabetic medications at baseline, n (%)	53 (80.3)	30 (96.8)	37 (90.2)
Lipid-lowering medications at baseline, n (%)	34 (51.5)	26 (83.9)	34 (82.9)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; LD, lipodystrophy; PL, partial lipodystrophy; ULN, upper limit of normal [a] PL subgroup, patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L			

Source: Study NIH 991265/20010769 CSR (9)

Table C17: Baseline characteristics for study FHA101

Characteristic	**GL (N = 9)**	**PL (N = 32)**	
		PL subgroup[a] (N = 7)	**Overall (N = 32)**
Female, n (%)	8 (88.9)	7 (100.0)	31 (96.9)
Race n (%)			
Caucasian	8 (88.9)	5 (71.4)	22 (68.8)
Black	1 (11.1)	2 (28.6)	3 (9.4)
Asian/Native American/Hispanic/Other	0/0/0/0	0/0/0/0	1 (3.1)/ 2 (6.3)/ 1 (3.1)/ 3 (9.4)
Age, median (range)	25.0 (9.0, 67.0)	42.0 (23.0, 57.0)	44.5 (23.0, 67.0)
<18 years	3 (33.3)	0	0
≥18 years	6 (66.7)	7 (100.0)	32 (100.0)
LD type			
Acquired	6 (66.7)	1 (14.3)	3 (9.4)
Congenital/Familial	2 (22.2)	6 (85.7)	29 (90.6)
BMI, kg/m^2, median (range)	21.3 (13.9, 38.4)	27.6 (20.9, 30.5)	30.3 (19.1, 41.2)
HbA1c, %			
Median (range)	8.4 (5.1, 10.2)	7.6 (5.7, 11.1)	8.0 (5.6, 12.8)
≥6.5, n (%)	6 (66.7)	6 (85.7)	27 (84.4)
≥8.0, n (%)	5 (55.6)	2 (28.6)	16 (50.0)
Fasting plasma glucose, mmol/L, median (range)	10.4 (4.2, 23.3)	7.4 (5.1, 13.4)	7.8 (2.0, 15.0)
Fasting triglycerides, mmol/L,			
Median (range)	3.3 (1.5, 119.9)	2.9 (0.7, 14.0)	3.2 (0.7, 50.4)
≥2.26 mmol/L	6 (66.7)	4 (57.1)	23 (71.9)
≥5.65 mmol/L	3 (33.3)	1 (14.3)	7 (21.9)
ALT, >ULN, n (%)	5 (55.6)	5 (71.4)	23 (71.9)
AST, >ULN, n (%)	4 (44.4)	2 (28.6)	9 (28.1)
Anti-diabetic medications at baseline, n (%)	2 (22.2)	6 (85.7)	19 (59.4)
Lipid-lowering medications at baseline, n (%)	2 (22.2)	6 (85.7)	19 (59.4)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; GL = generalised lipodystrophy; LD = lipodystrophy; HbA1c = glycated haemoglobin; PL = partial lipodystrophy; ULN = upper limit of normal

[a]PL subgroup = patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

Source: Study FHA101 CSR (10)

Baseline co-morbidities and medication history

In study NIH 991265/20010769 all 107 patients had at least one medical history event reported. The most commonly reported medical history findings in GL patients were hypertriglyceridaemia (71%) and diabetes mellitus (70%). Other relevant medical history included hepatomegaly/ hepatosplenomegaly (62%), NASH/steatohepatitis (52%), proteinuria (45%), pancreatitis (27%), and hepatic steatosis (24%).

Consistent with the severity of the defined PL subgroup, 94% of these patients had a history of hypertriglyceridaemia and 84% had diabetes mellitus. Hepatic steatosis and pancreatitis were each reported in 39% of PL subgroup patients and 26% had NASH or steatohepatitis.

The majority of patients in the GL group (80%) and PL subgroup (97%) were receiving antidiabetic medications at study entry (**Table C16**), with 59% and 55%, respectively, receiving insulin. Overall, 19 GL patients (15%) and 11 patients in the PL subgroup (35%) were receiving the U-500 form of insulin at study baseline, reflective of the severe insulin resistance that many of these patients have due to their disease. Lipid-lowering therapies were more commonly administered in patients in the PL subgroup (84%) compared to those with GL (52%) – reflective of the significant hypertriglyceridaemia in this subgroup of patients.

For study FHA101 only limited data were available for medical history and concomitant medications in this study as the data were only captured at one study site.

9.4.3.3 Methodology

Both study NIH 991265/20010769 and study FHA101 had a similar study design as they were both open-label, single-arm clinical trials designed to evaluate the safety and efficacy of metreleptin in patients with GL and PL. In both studies the efficacy of treatment was evaluated primarily by assessment of changes over time in HbA1c and fasting serum triglyceride levels. In study NIH 991265/20010769 changes in plasma glucose, liver volume, other lipid parameters (total cholesterol, LDL-C, HDL-C), and liver function tests (ALT and AST) were also evaluated as measures of the efficacy of treatment. As FHA101 was a treatment IND study, only HbA1c, glucose, triglycerides, and liver function tests were evaluated for efficacy.

9.4.3.4 Exposure

In study NIH 991265/20010769 most patients (54%) received metreleptin for more

than 3 years. Total patient-years of exposure were 328.3 years for the GL group and 121.3 years for the PL subgroup and median overall durations of treatment were 49.9 months and 29.3 months, respectively. The shorter duration of treatment in the PL subgroup is related to the fact that most PL patients, who, in general, have higher leptin levels, were not eligible for the study until 5 years after the start when the eligibility criteria were modified to increase eligible leptin levels.

The median weighted average daily dose over the study period in GL patients was 4.4 mg or 0.093 mg/kg and, consistent with the dosing recommendations, was lower in males (3.0 mg; 0.057 mg/kg) than females (5.0 mg; 0.099 mg/kg). For patients in the PL subgroup, the median weighted average daily dose over the study period (8.2 mg) was higher than the GL group; however, on a mg/kg basis, the median weighted average daily dose of 0.119 mg/kg was consistent with females in the GL group (all but 1 patient in the PL subgroup was female).

In study FHA101 median overall duration of treatment was 21.3 months for the 9 GL patients and 53.1 months for the 7 patients in the PL subgroup.

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

The NIH 991265/20010769 and FHA studies included a retrospective subgroup of patients with a diagnosis of PL and the more severe metabolic abnormalities according to the original indication being sought: HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L at baseline. This criteria, however, is likely to change in the final indication.

Study NIH 991265/20010769 included specific eligibility criteria for leptin levels (<12 ng/mL for females and <8 ng/mL for males >5 years). As study FHA101 did not have set leptin levels for study entry, the PL subgroup definition for this study required patients to have leptin levels <12 ng/mL to be consistent with the entry criteria for Study NIH 991265/20010769. Of note, only patients enrolled at one study site (the University of Michigan study site) had baseline leptin levels measured; all patients in the PL subgroup are from that single study site.

Pre-specified subgroup analyses were performed based on a number of baseline factors, including metabolic abnormalities, age, LD subtype, and region. The purpose of these comparisons was to show whether treatment effects are observed consistently across relevant populations. The results presented are primarily based on the pivotal study NIH 991265/20010769, where the sample size allows for comparison across most subgroups (Section 9.6.1.5). As study FHA101 evaluated only 9 GL patients and 7 patients in the PL subgroup, analyses across subgroups were limited in their conclusions. The statistical analysis plan (SAP) was finalised before the database lock.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Disposition for the 107 patients enrolled and treated in study NIH 991265/20010769 is summarised in

Table **C18**.

Table C18: Patient disposition for study NIH 991265/20010769

Disposition parameter	GL (N = 66)	PL (N = 41)	
		PL subgroup[a] (N = 31)	Overall (N = 41)
Total number of patients			
Treated	66	31	41
Premature discontinuation	23 (34.8)	11 (35.5)	15 (36.6)
Primary reason for premature Discontinuation			
Noncompliance	5 (7.6)	6 (19.4)	6 (14.6)
Death	3 (4.5)	1 (3.2)	1 (2.4)
Ineligibility determined	2 (3.0)	0	0
Adverse event	1 (1.5)	0	0
Lost to follow-up	1 (1.5)	0	0
Other:	11 (16.7)	4 (12.9)	8 (19.5)
Transferred to other program	8	1	2
Lack of efficacy/No benefit	1	3	5
Other[b]	2	0	1
Patients contacted for follow-up[c]	38 (57.6)	20 (64.5)	26 (63.4)

Abbreviations: GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; PL, partial lipodystrophy

[a] PL subgroup, patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] Other reasons included diagnosis of bipolar disorder; health issues, and off for gastric bypass surgery

[c] Patients who were on treatment at the time of approval of metreleptin in the US were contacted to determine if and how they were able to continue on therapy

Source: Study NIH 991265/20010769 CSR (9)

Disposition for the 41 patients enrolled and treated in study FHA101 is summarised in

Table C19.

Table C19: Patient disposition for study FHA101

Disposition parameter	GL (N = 9)	PL (N = 32)	
		PL subgroup[a] (N = 7)	Overall (N = 32)
Total number of patients			
Treated	9 (100.0)	7 (100.0)	32 (100.0)
Premature discontinuation	4 (44.4)	2 (28.6)	20 (62.5)
Primary reason for premature discontinuation			
Adverse event	0	0	3 (9.4)
Lost to follow-up	1 (11.1)	0	1 (3.1)
Death	1 (11.1)	0	1 (3.1)
Physician decision	1 (11.1)	1 (14.3)	6 (18.8)
Withdrawal by patient	1 (11.1)	1 (14.3)	9 (28.1)
Patients contacted for follow-up	2 (22.2)	0	4 (12.5)

Abbreviations: GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; PL,partial lipodystrophy

[a] PL subgroup, patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

Source: Study FHA101 CSR (10)

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

In study NIH 991265/20010769 approximately one-third of GL patients (35%) and patients in the PL subgroup (36%) discontinued treatment prior to the end of the study (

Table **C18**). The most common reason for discontinuation was patient noncompliance (5 GL patients, 8% and 6 PL subgroup patients, 19%).

In study FHA101, 4 (44%) of 9 GL patients and 2 (29%) of 7 patients in the PL subgroup, were reported to have discontinued treatment prior to the end of the study; all reasons for discontinuation were reported in 1 patient each (

Table C19).

9.5 Critical appraisal of relevant studies

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

A critical appraisal of study NIH 991265/20010769 and FHA101 are shown in **Table C20** and **Table C21**, respectively. The limitations of the studies, including the single-arm design, are discussed in Section 9.9.2.

Table C20: Critical appraisal of study NIH 991265/20010769

Study name: NIH 991265/20010769		
Study question	Response (yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	The patient population was representative of a defined population. The patients had low leptin levels (<12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years) and at least 1 metabolic abnormality out of diabetes mellitus; fasting insulin concentration >30 µU/mL, and/or fasting triglyceride concentration >2.26 mmol/L or postprandially elevated triglycerides >5.65 mmol/L when fasting was clinically not indicated (e.g., in infants); these are the hallmarks of this syndrome, i.e., insulin resistance with diabetes mellitus and hypertriglyceridaemia. Patients were recruited from different regions across the world.
Was the exposure accurately measured to minimise bias?	Yes	Exposure was clearly defined and accurately measured. The measurement of exposure was objective i.e dose and duration, including average (mean [SD], median and range) for daily dose (mg/day), and weighted average dose (mg/kg).
Was the outcome accurately measured to minimise bias?	Yes	The study's efficacy endpoints were objective measurements, including the co-primary endpoints of HbA1c and triglycerides. These measurements were primarily obtained at a single laboratory and thus treatment effects could be appropriately evaluated. The efficacy endpoints were clinically relevant to the patient and the progression of disease.
Have the authors identified all important confounding factors?	Yes	Potential confounding factors included: concomitant medication use, sex, race, age, weight, height, body weight category, BMI, region, LD subtype (CGL, AGL, FPL, APL), gene mutation (LMNA, PPARg, Seipin, AGPAT-2, ZMPSTE24, Other, and not applicable), baseline laboratory values.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	In addition to the FAS, efficacy was analysed on the CFAS, which included all patients in the FAS who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid lowering therapies), prior to Month 12. Data for all anti-diabetic or lipid lowering therapies, including type, dose, regimen, and route of administration, underwent medical review and patients who had these types of medications added or doses increased that may have had an impact on the efficacy endpoints were excluded from the CFAS. Patients were excluded separately based on the type of medication that was added or increased, e.g., patients with potentially confounding anti-diabetes medications were excluded

		from the analyses of HbA1c and those with potentially confounding lipid-lowering therapies were excluded from analyses of triglycerides. In general, the results for the efficacy analyses were consistent for the FAS and the CFAS.
In addition, subgroup analysis were conducted based on a number of baseline characteristics to show whether treatment effects were observed consistently across relevant populations. including: LD subtype (AGL, CGL, FPL, and APL); age (age categories <6, ≥6 to <12, ≥12 to <18, < 18, and ≥18 years old); region (US, EU, EU and Eastern Mediterranean, and Other); presence of metabolic abnormalities at baseline (HbA1c [<6.5 and ≥6.5%], ≥7%, ≥8% and fasting triglycerides [<2.26 mmol/L and ≥2.26 mmol/L / <200 and		
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		
Abbreviations: AGL, acquired generalised lipodystrophy; APL, acquired partial lipodystrophy; BMI, body mass index; CFAS, Controlled Concomitant Medication Full Analysis Set; CGL, congenital generalised lipodystrophy; CI, confidence interval; EU, European Union; FAS, full analysis set; FPL, familial partial lipodystrophy; GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; LD, lipodystrophy; LOCF, last observation carried forward; PL, partial lipodystrophy; SD, standard deviation; US, United States		

Source: Study NIH 991265/20010769 CSR(9)

Table C21: Critical appraisal of study FHA101

Study name: FHA101		
Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	The patient population was representative of a defined population. Patients had to have been diagnosed with at least 1 of the following 2 metabolic disorders: diabetes mellitus and/or hypertriglyceridaemia as defined by fasting triglyceride concentrations >2.26 mmol/L (>200 mg/dL), which are the hallmark of this syndrome
Was the exposure accurately measured to minimise bias?	Yes	Exposure was clearly defined and accurately measured. The measurement of exposure was objective i.e dose and duration, including average (mean [SD], median and range) for daily dose (mg/day), weighted average dose (mg/kg).
Was the outcome accurately measured to minimise bias?	Yes	The study's efficacy endpoints were objective measurements, including the co-primary endpoints of HbA1c and triglycerides. These measurements were primarily obtained at a single laboratory and thus treatment effects could be appropriately evaluated. The efficacy endpoints were clinically relevant to the patient and the progression of disease.
Have the authors identified all important confounding factors?	Yes	Potential confounding factors included: concomitant medication use, sex, race, age, weight, height, body weight category, BMI, region (US, EU, EU and Eastern Mediterranean, other), LD subtype (CGL, AGL, FPL, APL), gene mutation (LMNA, PPARg, Seipin, AGPAT-2, ZMPSTE24, Other, and Not Applicable), baseline laboratory values

Have the authors taken account of the confounding factors in the design and/or analysis?	Partially	As in study NIH 991265/20010769 efficacy was analysed on the FAS and the CFAS, which included all patients in the FAS who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid lowering therapies), prior to Month 12. In general, the results for the efficacy analyses were consistent for the FAS and the CFAS.
Was the follow-up of patients complete?	Yes	Only two patients were lost to follow-up (see Section 9.4.5)
How precise (for example, in terms of confidence interval and p values) are the results?	Due to the small sample sizes, the 95% CIs were wide	The following results with 95% CIs were reported were reported: GL patients: mean change from baseline to Month 12/LOCF for HbA1c was -1.2 % (95% CI: -4.3, 2.0) and the mean percent change in triglycerides was -26.9% (-124.1, 70.4) PL subgroup patients (excluding outlier patient): mean change from baseline to Month 12/LOCF for HbA1c was -0.9% (95% CI: -1.4, -0.4) and the mean percent change in triglycerides was -8.5% (-36.4, 19.5).
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		
Abbreviations: AGL, acquired generalised lipodystrophy; APL = aquired partial lipodystrophy; BMI = body mass index; CFAS = Controlled Concomitant Medication Full Analysis Set; CGL = congenital generalised lipodystrophy; CI = confidence interval; EU = European Union; FAS = full analysis set; FPL = familial partial lipodystrophy; GL = generalised lipodystrophy; HbA1c = glycated haemoglobin; LD = lipodystrophy; LOCF = last observation carried forward; PL = partial lipodystrophy; SD = standard deviation; US = United States		

Source: Study FHA101 CSR (10)

9.6 Results of the relevant studies

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

9.6.1.1 NIH 991265/20010769 study results

A summary of the primary endpoints, key secondary endpoints and other secondary endpoints of relevance is shown in **Table C22**, and described in more detail below. In addition, other endpoints of relevance are described below including liver pathology (Section 9.6.1.4.3), effect on hyperphagia (satiety) (Section 9.6.1.4.4), concomitant medication use (Section 9.6.1.4.5), growth and pubertal status (Section 9.6.1.4.6), and subgroup analysis (Section 9.6.1.5). Adverse events (AEs), including deaths and cases of pancreatitis and infections, are described in Section 9.7.

Table C22: Outcomes from study NIH 991265/20010769

Study name		NIH 991265/20010769		
Size of study groups	**Treatment**	GL = 62 PL subgroup[a] = 30 PL overall = 40		
Study duration	**Time unit**	12 months		
Type of analysis	**Intention-to - treat/per protocol**	FAS: all patients who received at least 1 dose of study drug and who had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit		
Co-primary endpoint: Change from baseline in HbA1c (%) using LOCF (FAS population, excluding outlier patient[b])				
		GL	PL subgroup	PL overall

		N = 62	N = 29[a,b]	N = 39[b]
Baseline value	**n**	62	29	39
	Mean (SD)	8.6 (2.33)	8.8 (1.91)	8.0 (2.18)
Month 12 value, LOCF	**n**	59	27	36
	Mean (SD)	6.4 (1.68)	8.0 (1.83)	7.5 (1.84)
Effect size: actual change from baseline	**n**	59	27	36
	Mean (SD)	-2.2 (2.15)	-0.9 (1.23)	-0.6 (1.22)
	95% CI	-2.7, -1.6	-1.4, -0.4	-1.0, -0.2
Statistical test	**Type**	P values computed using paired t-tests		
	p value	<0.001	<0.001	0.005
Co-primary endpoint: Change from baseline in triglycerides (mmol/L) using LOCF (FAS population, excluding outlier patient[b])				
		GL N = 62	PL subgroup N = 29[a, b]	PL overall N = 39[b]
Baseline value	**n**			
	Mean (SD)	14.7 (25.66)	15.7 (26.42)	12.5 (23.35)
Month 12 value, LOCF	**n**			
	Mean (SD)	4.5 (6.10)	6.0 (8.41)	5.4 (7.37)
Effect size: percent change from baseline	**n**	57	27	36
	Mean (SD)	-32.1 (71.28)	-37.4 (30.81)	-20.8 (47.93)
	95% CI	-51.0, -13.2	-57.2, -8.6	-51.0, -13.2
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.001	<0.001	0.013
Key secondary endpoint: Actual and percent change from baseline in fasting plasma glucose levels at Month 12 (mmol/L) using LOCF (FAS population)				
		GL N = 62	PL subgroup N = 30[a]	PL overall N = 40
Baseline value	**n**			
	Mean (SD)	10.2 (5.05)	10.0 (4.36)	8.8 (4.39)
Month 12 value, LOCF	**n**	59	28	37
	Mean (SD)	7.0 (3.40)	8.1 (3.55)	7.5 (3.28)
Effect size: actual change from baseline	**n**	59	28	37
	Mean (SD)	-3.0 (4.72)	-1.8 (2.83)	-1.2 (2.69)
	95% CI	-4.2, -1.7	-2.9, -0.7	-2.1, -0.3
Statistical test	**Type**	P values computed using paired t-tests		
	p value	<0.001	0.003	0.012
Effect size: percent change from baseline	**n**	59	28	37
	Mean (SD)	-19.7 (37.21)	-13.2 (28.99)	-6.1 (29.59)
	95% CI	-29.4, -10.0	-24.4, -1.9	-16.0, 3.8
Statistical test	**Type**	P values computed using paired t-tests		
	p value	<0.001	0.023	0.219
Key secondary endpoint: Responder analysis: patients who met target reductions in HbA1c or triglycerides at Month 12/LOCF (FAS population)				
		GL	PL subgroup	PL overall

		N = 62	N = 30[a]	N = 40
≥1% actual decrease in HbA1c or ≥30% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	47/59 (79.7)	19/28 (67.9)	19/37 (51.4)
	95% CI[c]	(67.2, 89.0)	(47.7, 84.1)	(34.4, 68.1)
≥1.5% actual decrease in HbA1c or ≥35% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	44/59 (74.6)	14/28 (50.0)	14/37 (37.8)
	95% CI[c]	61.6, 85.0	30.7, 69.4	22.5, 55.2
≥2% actual decrease in HbA1c or ≥40% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	39/59 (66.1)	12/28 (42.9)	12/37 (32.4)
	95% CI[c]	52.6, 77.9	24.5, 62.8	18.0, 49.8
Other secondary endpoints: Change from baseline to Month 12/LOCF in fasting lipids (FAS population)				
		GL N = 62	PL subgroup N = 30[a]	PL overall N = 40
Total cholesterol (mmol/L)				
Baseline	**n**	62	30	40
	Mean (SD)	5.9 (3.66)	6.4 (2.80)	5.9 (2.62)
Actual change from **baseline**	**n**	41	21	30
	Mean (SD)	-2.3 (2.91)	-0.9 (1.52)	-0.6 (1.45)
LDL-C (mmol/L)				
Baseline	**n**	37	17	24
	Mean (SD)	2.6 (1.35)	2.8 (1.02)	2.6 (1.01)
Actual change from **baseline**	**n**	22	12	18
	Mean (SD)	-0.9 (1.29)	-0.3 (0.66)	-0.1 (0.62)
HDL-C (mmol/L)				
Baseline	**n**	56	25	35
	Mean (SD)	0.7 (0.25)	0.8 (0.23)	0.8 (0.21)
Actual Change from **BL**	**n**	35	17	26
	Mean (SD)	-0.0 (0.24)	0.0 (0.14)	0.0 (0.14)
Other secondary endpoints: Change from baseline to Month 12 in liver transaminase levels (FAS Population)				
		GL N = 62	PL subgroup N = 30[a]	PL overall N = 40
ALT (U/L)				
Baseline	**n**	62	30	40
	Mean (SD)	111.9 (112.62)	39.2 (28.02)	54.8 (57.99)
Actual change from **baseline**	**n**	41	21	30
	Mean (SD)	-53.1 (126.56)	-5.0 (11.95)	-0.4 (26.95)
AST (U/L)				
Baseline	**n**	62	30	40
	Mean (SD)	75.0 (71.07)	31.9 (19.64)	38.4 (33.46)
Actual change from **baseline**	**n**	41	21	30
	Mean (SD)	-23.8 (142.38)	-6.0 (14.77)	-5.1 (21.06)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FAS, full				

analysis set; GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LOCF, last observation carried forward; PL, partial lipodystrophy; SD, standard deviation

[a] PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] Excluding results for Patient 901-080 who had an outlier value for percent increase from baseline in triglycerides of >1000% at Month 12/LOCF. The patient was terminated from treatment by the Investigator for noncompliance with dosing

Source: Study NIH 991265/20010769 CSR (9)

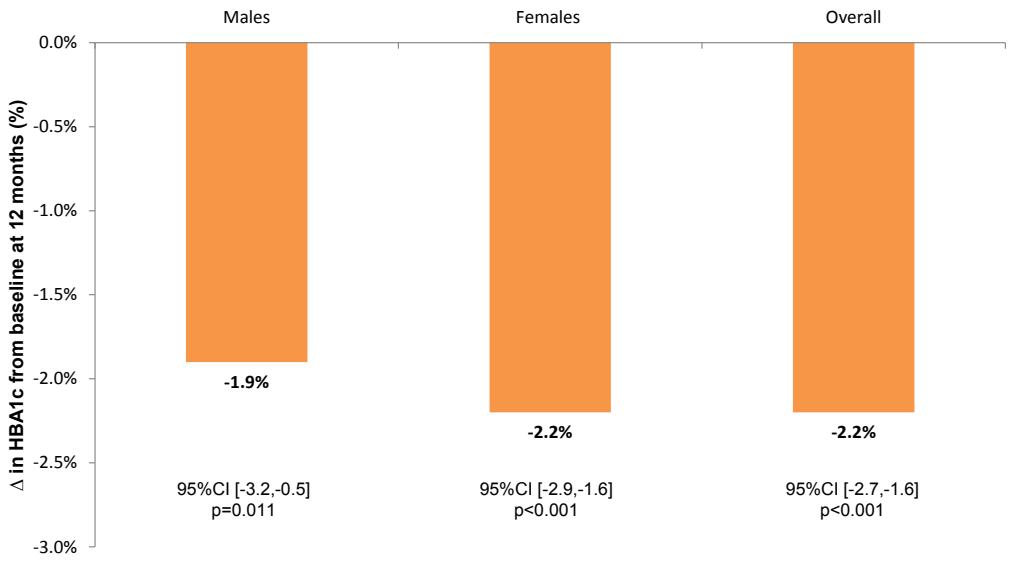
9.6.1.2 Co-primary efficacy endpoints: effect of metreleptin on change from baseline in HbA1c and percent change from baseline in triglycerides

Treatment with metreleptin led to clinically meaningful and statistically significant improvements in glycaemic control and hypertriglyceridaemia in patients with GL and in the PL subgroup.

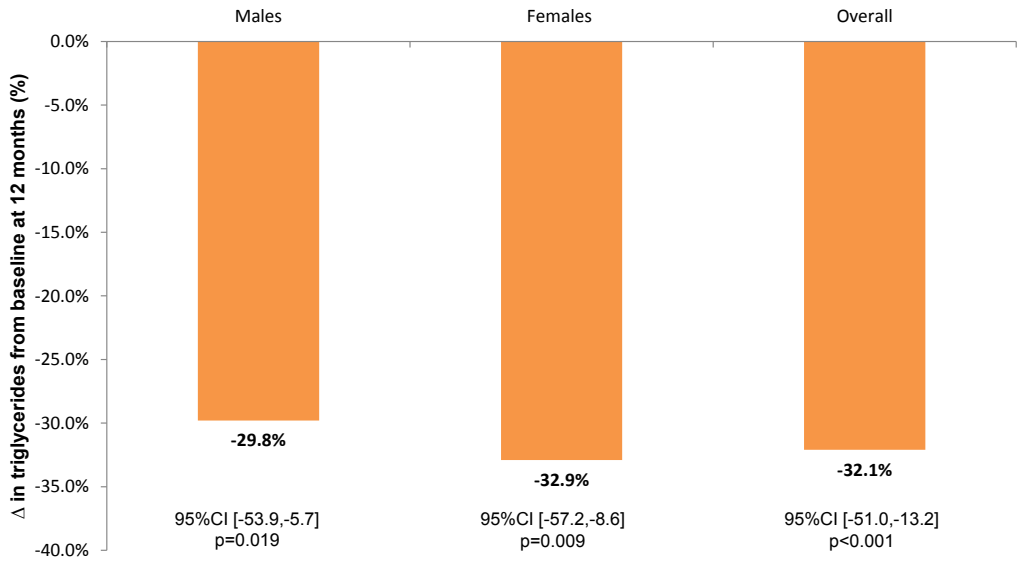
For GL patients, the changes from baseline to Month 12/LOCF were clinically meaningful and statistically significant for HbA1c, with a mean change of -2.2% (p<0.001), and for triglycerides, with a mean percent change of -32.1% (p=0.001) (**Table C22 Figure C17**). Both males and females with GL sustained clinically meaningful and statistically significant reductions in HbA1c and triglycerides at Month 12/LOCF (**Figure C17**).

Figure C17: Mean change in (a) HbA1c and (b) triglycerides from baseline at month 12/LOCF in patients with GL treated with metreleptin in study NIH 991265/20010769

(a)



(b)

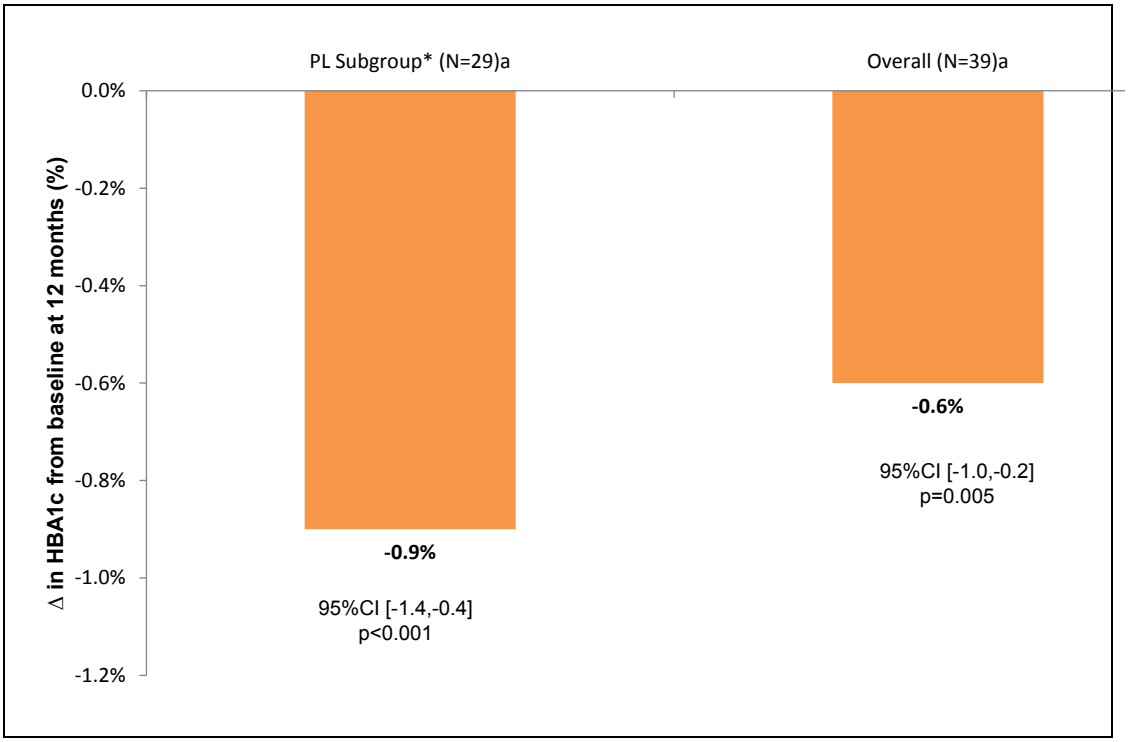


Abbreviations: CI, confidence interval; GL, generalised lipodystrophy; HbA1c, glycated haemoglobin
Source: Created using data from the study NIH 991265/20010769 CSR(9)

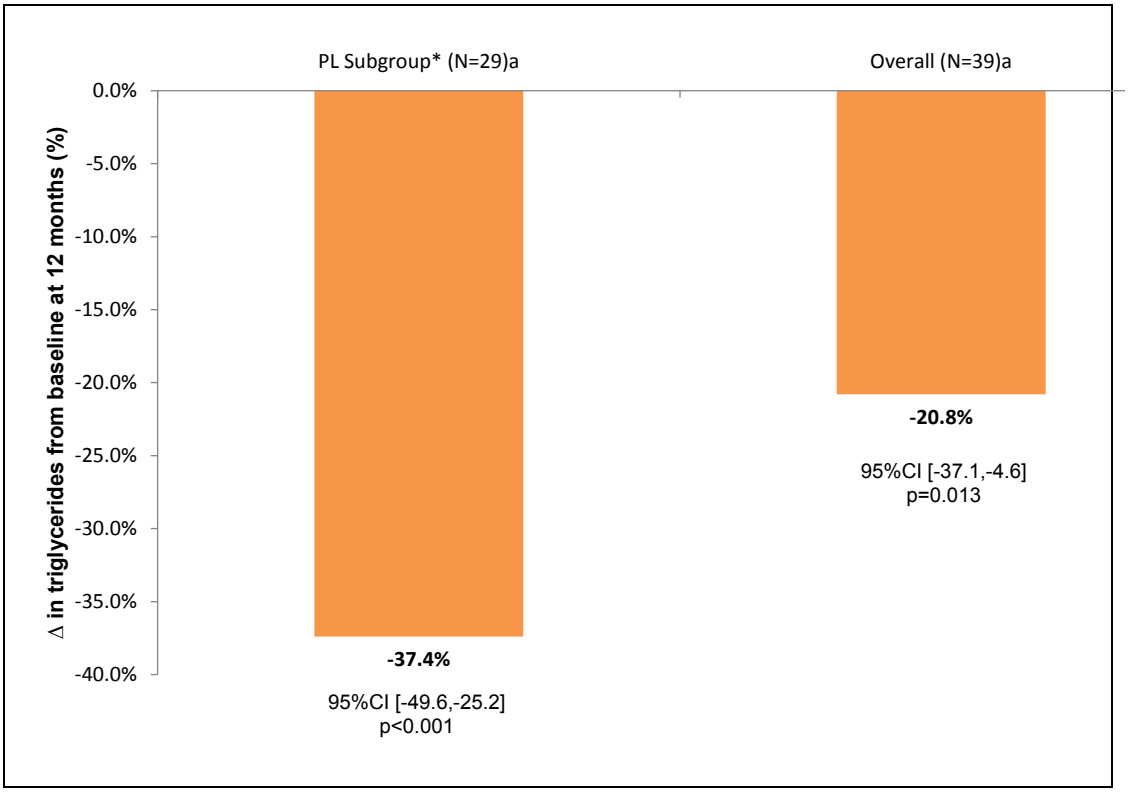
For patients in the PL subgroup, treatment with metreleptin also led to clinically meaningful and statistically significant reductions in HbA1c with a mean change of -0.9% (p<0.001). However, due to an extreme outlying result for one patient as explained below, results for triglycerides in the overall PL subgroup showed a small mean percent increase between baseline and Month 12/LOCF for the FAS. The outlying result was observed in a patient who had a >1000% increase in triglycerides to the primary endpoint; the only patient in the study with this level of change at Month 12. This patient was terminated from the study by the Investigator 2 days prior to the Month 12 assessment for noncompliance with study drug administration. When the data for this noncompliant patient are excluded from analysis, the results for mean percent change from baseline to Month 12/LOCF in triglycerides for the PL subgroup showed a clinically meaningful and statistically significant change of -37.4% (p<0.001), which was consistent with the results observed for the GL group (**Figure C17**, **Figure C18**).

Figure C18: Mean change in (a) HbA1c and (b) triglycerides from baseline at month 12/LOCF in patients with PL treated with metreleptin in study NIH 991265/20010769

(a)


PL Subgroup* (N=29)a
Overall (N=39)a
0.0%
-0.2%
-0.4%
-0.6%
-0.8%
-1.0%
-1.2%
Δ in HBA1c from baseline at 12 months (%)
-0.9%
95%CI [-1.4,-0.4]
p<0.001
-0.6%
95%CI [-1.0,-0.2]
p=0.005

(b)



Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; PL, partial lipodystrophy

* Patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

[a] Excluding results for Patient 901-080 who had an outlier value for percent increase from baseline in triglycerides of >1000% at Month 12/LOCF. The patient was terminated from treatment by the Investigator for noncompliance with dosing

Source: Created using data from the study NIH 991265/20010769 CSR (9)

9.6.1.3 Key secondary endpoints

9.6.1.3.1 Actual and percent change from baseline in fasting plasma glucose levels at Month 12

Among the patients with GL, treatment with metreleptin led to clinically meaningful and statistically significant reductions from baseline to Month 12/LOCF in fasting glucose with a mean change of -3.0 mmol/L (p<0.001), representing a 20% decrease in fasting glucose levels (**Table C22**).(9) Results in the PL subgroup were similar to the GL group with a mean change from baseline to Month 12/LOCF in fasting glucose of -1.8 mmol/L (p=0.003), representing a 13% decrease from baseline.(9)

9.6.1.3.2 Responder analyses: Patients achieving target reductions in HbA1c and triglycerides

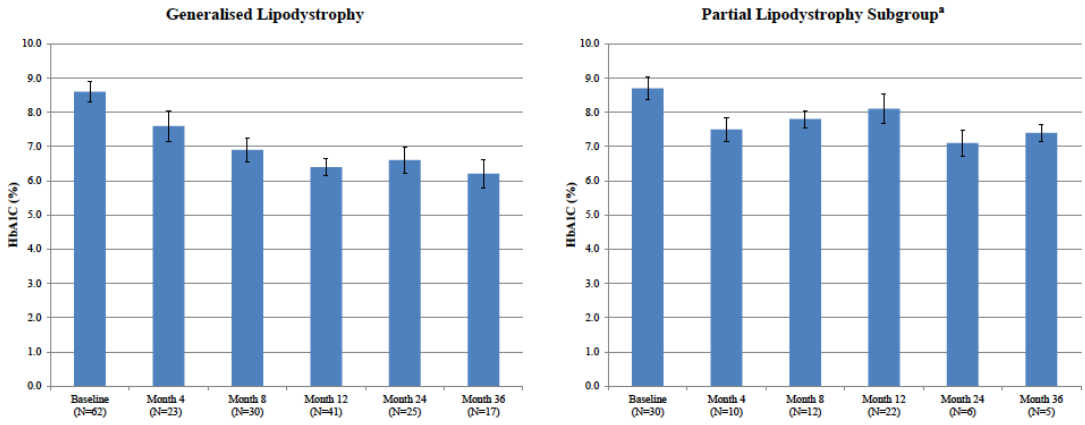
Nearly 80% of patients with GL achieved a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 66% achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides at that time.(9) Results were consistent in the PL subgroup, with 68% of patients achieving a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF and 43% achieving the highest target decreases of ≥2% in HbA1c or ≥40% in triglycerides.(9)

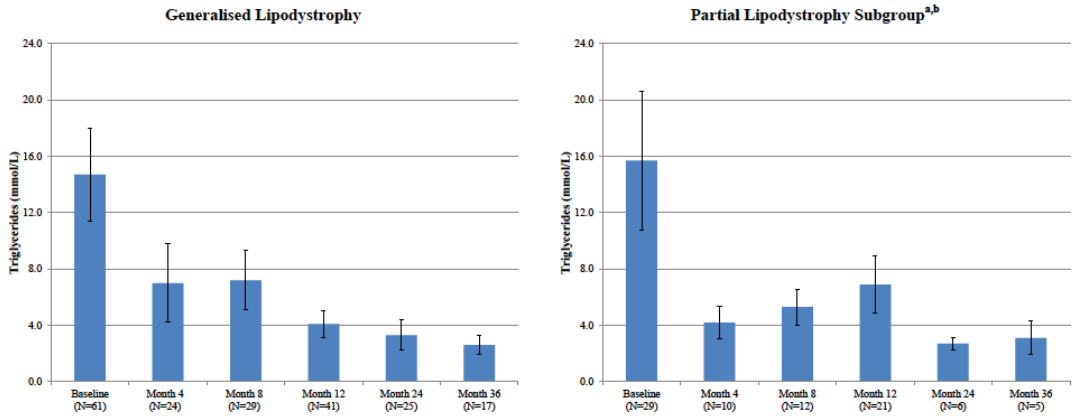
9.6.1.4 Other endpoints of relevance

9.6.1.4.1 Analysis of change over time in HbA1c and triglycerides: persistence of efficacy

Long-term treatment with metreleptin led to clinically meaningful and statistically significant reductions in HbA1c and triglycerides in patients with GL and in the PL subgroup. Graphic displays of mean levels through Month 36 for HbA1c and triglycerides are provided in **Figure C19**.

Figure C19: Mean (SEM) change in (a) HbA1c (%) and (b) triglycerides (mmol/L; excluding outlier patient) at baseline and months 4, 8, 12, 24 and 36 of metreleptin treatment (FAS population) in study NIH 991265/20010769





Abbreviations: FAS, Full Analysis Set; HbA1c, glycated haemoglobin; PL,partial lipodystrophy; SEM, standard error of the mean

[a] PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] Excluding results for Patient 901-080 who had an outlier value for percent increase from baseline in triglycerides of >1000% at Month 12/LOCF. The patient was terminated from treatment by the Investigator for noncompliance with dosing

Source: Study NIH 991265/20010769 CSR.(9)

Least-squares mean (LS mean) changes from baseline in HbA1c in the GL group based on a mixed model repeated measures (MMRM) analysis were -2.3%, -2.1% and -1.5% at Months 12, 24 and 36, respectively.(9) Importantly, the overall MMRM analysis, which evaluates average levels across all visits, showed a statistically significant decrease from baseline for GL patients with an LS mean change of -1.4% ($p<0.001$). Results were similar in the PL subgroup with LS mean changes in HbA1c of -0.9%, -1.3%, and -1.0% at Months 12, 24, and 36 and an overall LS mean change of -0.6% ($p<0.001$).

In the GL group, LS mean percent changes from baseline in triglycerides were -48.3%, -22.6% and -40.6% at Months 12, 24, and 36, respectively; based on the overall MMRM analysis, the LS mean change in triglycerides was -22.4% ($p<0.001$). For the PL subgroup (excluding data from Patient 901-080), LS mean percent changes in triglycerides were -36.2%, -31.7%, and -13.7% at Months 12, 24 and 36, respectively, with an overall LS mean change of -18.6% ($p=0.004$).

9.6.1.4.2 Change from baseline in fasting lipids at Month 12

Changes in total cholesterol, LDL-C and HDL-C were consistent with those for triglycerides. In the GL group, mean changes to Month 12/LOCF for total cholesterol and LDL-C were -2.3 and -0.9 mmol/L, respectively, representing mean percent changes of -28% and -24% **Table C22**).(9) In the PL subgroup, mean change in total cholesterol to Month 12/LOCF was -0.9 mmol/L (-11% change) and in LDL-C was -0.3 mmol/L (-4% change). Little to no change from baseline was noted for HDL-C in either group (**Table C22Error! Reference source not found.**).

9.6.1.4.3 Effect of metreleptin on hepatic enzymes, liver volume, and liver pathology

Because of the ectopic fat deposition in the liver, patients very commonly present with NASH-induced elevations in transaminase levels and hepatomegaly. Improvements in both liver function tests and liver volume were noted in GL patients and in patients in the PL subgroup.

As noted in **Table C16**, most patients in the GL group entered the study with elevated hepatic transaminase levels (74% with ALT >upper limit of normal (ULN) and 55% with AST >ULN). Substantial reductions in both ALT and AST occurred during treatment with metreleptin in patients with GL. In the 41 GL patients with hepatic data available, the mean changes at Month 12/LOCF in ALT versus baseline was -53.1 U/L and AST versus baseline was -23.8 U/L.(9) Reductions in transaminase levels were also observed in the PL subgroup, although of lower magnitude than that in the GL group; this is likely related to lower baseline levels of ALT and AST in this group of patients (29% and 23% with ALT and AST >ULN, respectively; **Table C16**).(9) In the PL subgroup, mean changes to Month 12/LOCF in ALT and AST were -5.0 U/L and -6.0 U/L, respectively.

A total of 21 patients with GL and 8 patients in the PL subgroup had liver volume assessed at baseline and at least one post-baseline assessment.(9) Most of these patients had hepatomegaly with liver volumes >2000 mL, including 20 of 21 patients with GL and 6 of 8 patients in the PL subgroup. Reductions in liver volume were observed at all post-baseline assessments in 15 (71%) of the 21 patients with GL who could be assessed for changes from baseline and an additional 4 patients had reductions at all assessments on or after Month 12. Reductions in liver volume for these 19 patients ranged from 7% to 71%, with most patients (12 of 19) having reductions of ≥30%. Among the 8 patients in the PL subgroup, 4 (50%) had reductions observed at all post-baseline assessments and an additional patient had reductions at all assessments on or after Month 12. Reductions in liver volume for these 5 patients ranged from 8% to 51%.

Importantly, among paediatric patients, reductions from baseline were observed at all assessments in 10 (77%) of 13 patients with data available, all with GL; the remaining 3 patients had reductions at all assessments after Month 12. Reductions ranged from 7% to 64% with most of these paediatric patients (8 of 13) having reductions ≥30%.(9)

Results of paired liver biopsies from patients in Study NIH 991265/20010769 were reported in the publication by Safar-Zadeh et al; significant improvements were observed in steatosis grade and ballooning injury scores with a reduction in the NAFLD activity score during long-term treatment with metreleptin in patients with NASH.(58) Patients with liver fibrosis at baseline remained stable on metreleptin.(58)

9.6.1.4.4 Effect of metreleptin on hyperphagia

One important effect of metreleptin in patients with LD is to decrease the marked hyperphagia that is observed in patients with GL and PL. As reported by Moran and colleagues from the NIH, metreleptin treatment of 14 patients with LD (12 with GL and 2 with PL) dramatically decreased food intake at 4 months from 3,170 kcal/day to 1,739 kcal/day.(55) In another evaluation in 8 patients treated in Study NIH 991265, satiation (the time to voluntary cessation of eating from a standardised food array after a 12-hour fast) and satiety (the time to hunger sufficient to consume a complete meal after consumption of a standardised preload) were evaluated. Metreleptin treatment decreased satiation time, increased satiety time, decreased energy consumed to produce satiation, and decreased the amount of food desired in the postabsorptive state.(54)

9.6.1.4.5 Effect of metreleptin treatment on concomitant medication use

A review was conducted on the data to determine if patients could discontinue use of insulin, oral antidiabetics, or lipid-lowering therapies after initiating treatment with metreleptin. Sixteen (41%) of 39 patients with GL who were receiving insulin at baseline were able to discontinue insulin use altogether after starting metreleptin as were 7 (22%) of 32 patients who were receiving oral antidiabetic medications at baseline. Among the 34 patients who were receiving lipid-lowering therapies at baseline, 8 (24%) were able to discontinue these medications. Many of these patients could discontinue the use of these therapies within the first 12 months of metreleptin treatment. In the PL subgroup, 1 patient was able to discontinue the use of oral antidiabetic medications and 1 was able to discontinue the use of lipid-lowering therapies.

9.6.1.4.6 Effect of metreleptin treatment on growth and pubertal status

Growth stature was assessed at screening/baseline and at least 1 post-baseline time point in 40 patients <18 years of age, including 36 patients with GL and 4 patients with PL, including 2 in the PL subgroup. Among the 36 GL patients, 22 were reported to have normal stature at study entry, 10 had tall stature for their age, and 4 had short stature. Overall 16 (44%) of the 36 patients were reported to have had growth complete or near complete prior to entry. Among the other 20 patients, 10 were reported to have normal growth (including 5 with normal stature, 3 who were tall and 2 who were short at baseline), 2 had growth acceleration (1 with normal stature and 1 with short stature), and 8 had growth deceleration (5 with normal stature and 3 who were tall). Among the 4 PL patients with data available, 2 patients (in the PL subgroup) had growth complete or near complete at study entry. Among the other 2 patients, 1 had short stature at baseline with growth deceleration reported on metreleptin and 1 had tall stature at baseline with normal growth on metreleptin.

Overall 33 patients <18 years of age had pubertal status assessed at baseline, including 27 patients with GL and 6 patients with PL (5 in the PL subgroup); 26 of these patients had puberty complete, near complete, or likely complete (based on growth data) prior to metreleptin. Among the other 7 patients, all with GL, 4 had

delayed puberty prior to metreleptin and 3 had precocious puberty; follow-up was available for 3 of these patients, all with delayed puberty at entry – 2 had normal development on metreleptin and 1 continued to have delayed puberty. Among the 14 patients without baseline data reported who were not prepubertal (normal for age), 13 reported normal pubertal onset and/or progression on metreleptin at a post-baseline assessment and 1 had delayed onset reported.

9.6.1.5 Subgroup analysis

Analyses for the evaluation of efficacy were conducted on pre-specified patient subgroups based on a number of factors, including baseline metabolic abnormalities, age, LD subtype, and region. A summary of the key findings from the subgroup analyses are shown in Table C23.

Table C23: Change from baseline to Month 12/LOCF in HbA1c and fasting triglycerides using LOCF for patient subgroups (FAS Population)

	GL				PL subgroup[a,b]			
	HbA1c		Triglycerides		HbA1c		Triglycerides	
	N	**Mean (SD) actual Δ to Month 12**	N	**Mean (SD) percent Δ to Month 12**	N	**Mean (SD) actual Δ to Month 12**	N	**Mean (SD) percent Δ to Month 12**
Baseline HbA1c (%):								
<6.5	14	-0.1 (0.35)	14	-4.1 (55.58)	2	0.1 (0.64)	2	-40.8 (27.29)
≥6.5	45	-2.8 (2.08)	43	-41.2 (73.97)	25	-1.0 (1.24)	25	-37.1 (31.57)
≥7	45	-2.8 (2.08)	43	-41.2 (73.97)	23	-1.1 (1.28)	23	-37.2 (32.95)
≥8	39	-3.0 (2.13)	37	-38.6 (78.36)	18	-1.3 (1.33)	18	-43.6 (33.60)
Baseline triglycerides (mmol/L):								
<2.26	13	-1.6 (1.71)	13	6.7 (44.20)	3	-0.9 (0.36)	3	-20.7 (28.33)
≥2.26	45	-2.3 (2.28)	45	-42.5 (73.87)	24	-0.9 (1.31)	24	-39.5 (31.03)
≥5.65	24	-3.3 (2.56)	24	-72.0 (25.09)	15	-1.0 (1.62)	15	-53.7 (25.21)
LD type								
Congenital/ Familial	40	-1.8 (1.92)	39	-22.2 (80.54)	23	-0.7 (0.88)	23	-37.4 (26.64)
Acquired	19	-2.9 (2.47)	18	-53.5 (39.09)	4	-2.0 (2.42)	4	-37.0 (54.98)
Age (years)								
< 6	5	0.2 (0.60)	5	-10.5 (58.18)	0	NA	0	NA
≥6 to <12	11	-1.1 (1.51)	11	-14.1 (49.74)	0	NA	0	NA

	GL				PL subgroup[a,b]			
	HbA1c		Triglycerides		HbA1c		Triglycerides	
	N	**Mean (SD) actual Δ to Month 12**	N	**Mean (SD) percent Δ to Month 12**	N	**Mean (SD) actual Δ to Month 12**	N	**Mean (SD) percent Δ to Month 12**
≥12 to <18	24	-2.6 (1.89)	23	-42.9 (45.55)	5	-0.6 (1.24)	5	-50.6 (33.62)
≥18	19	-2.8 (2.46)	18	-35.3 (106.23)	22	-1.0 (1.25)	22	-34.4 (30.15)
Region[c]								
US	34	-1.9 (2.02)	34	-23.2 (85.87)	20	-1.0 (1.32)	20	-41.8 (27.97)
EU and EM	11	-2.6 (1.96)	11	-52.1 (41.84)	2	-0.7 (0.28)	2	13.3 (38.20)
EU	7	-1.5 (1.45)	7	-38.7 (48.04)	1	-0.5 (NA)	1	40.3 (NA)
Other	12	-2.6 (2.81)	11	-39.5 (39.99)	5	-0.8 (1.23)	5	-39.8 (26.45)

Abbreviations: Δ**,** change; EU, European Union, EM, Eastern Mediterranean; FAS, Full Analysis Set; GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; NA, non-applicable; PL, partial lipodystrophy; SD, standard deviation; US, United States

[a] PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] Excluding results for Patient 901-080 who had an outlier value for percent increase from baseline in triglycerides of >1000% at Month 12/LOCF. The patient was terminated from treatment by the Investigator for noncompliance with dosing (Study NIH 991265/20010769, Listing 16.2.1.1)

[c] EU includes Belgium, UK, Germany, Italy, Lithuania, and Spain; EM includes Turkey, Albania, Israel, and Serbia; Other includes Argentina, Canada, India, Madagascar, Pakistan, Peru, and Saudi Arabia

Source: Study NIH 991265/20010769 CSR.(9)

Patients with more abnormal metabolic abnormalities at baseline achieved greater mean decreases from baseline to the primary time point of Month 12/LOCF. Among 45 patients with GL who had a baseline HbA1c of 7% or greater and data available at Month 12, the mean (SD) baseline HbA1c was 9.6% (1.63) and the mean reduction in HbA1c at Month 12 was 2.8%. Among 24 patients with GL who had a baseline triglyceride level 5.65 mml/l or greater and data available at Month 12, the mean (SD) baseline triglyceride level was 31.7 mmol/l (33.68) and the mean percent reduction in triglycerides at Month 12 was 72%. Among 15 patients in the subgroup with PL who had a baseline triglyceride level 5.65 mmol/l or greater and data available at Month 12, the mean (SD) baseline triglyceride level was 27.6 mmol/l (32.88) and the mean percent reduction in triglycerides at Month 12 was 53.7%.

Patients with the acquired form of LD generally achieved larger mean decreases from baseline compared with patients who had the congenital/familial form; although all groups showed reductions in HbA1c and triglycerides. This difference was related to higher baseline levels of HbA1c and triglycerides in patients with AGL and APL. In general, older patients who had higher levels of HbA1c and triglycerides at baseline had larger mean decreases from baseline than younger patients. However, patients in the younger age groups also showed improvement in metabolic abnormalities. Efficacy results were generally similar across region, although the small sample size for some regions precluded definitive conclusions.

9.6.1.6 FHA101 study results: supportive evidence

In general, the efficacy results in the supportive study FHA101 were consistent with those reported for study NIH 991265/20010769, although the number of patients included in analyses for this study was small. A summary of the results is shown in Table C24 and described in more detail in the following sections.

Table C24: Outcomes from study FHA101

Study name		FHA101		
Size of study groups	**Treatment**	GL = 9 PL subgroup[a] = 7 PL overall = 29		
Study duration	**Time unit**	12 months		
Type of analysis	**Intention-to - treat/per protocol**	FAS: all patients who received at least 1 dose of study drug and who had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit		
Co-primary endpoint: Change from baseline in HbA1c (%) using LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
Baseline value	**n**	9	7	29
	Mean (SD)	7.7 (1.99)	7.8 (1.71)	8.1 (1.77)
Month 12 value, LOCF	**n**	5	7	26
	Mean (SD)	6.2 (1.96)	7.0 (0.76)	7.8 (1.76)
	n	5	7	26
	Mean (SD)	-1.2 (2.53)	-0.8 (1.85)	-0.4 (1.49)

Effect size: actual change from baseline	**95% CI**	-4.3, 2.0	-2.5, 0.9	-1.0, 0.2
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.360	0.289	0.210
Co-primary endpoint: Change from baseline in triglycerides (mmol/L) using LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
Baseline value	**n**	8	7	29
	Mean (SD)	19.9 (40.90)	4.0 (4.54)	8.5 (12.37)
Month 12 value, LOCF	**n**	6	7	26
	Mean (SD)	7.6 (11.10)	3.6 (3.57)	6.4 (10.06)
Effect size: percent change from baseline	**n**	5	7	26
	Mean (SD)	-26.9 (78.32)	-8.5 (30.22)	8.7 (93.39)
	95% CI	-124.1, 70.4	-36.4, 19.5	-29.1, 46.4
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.486	0.485	0.640
Key secondary endpoint: Actual and percent change from baseline in fasting plasma glucose levels at Month 12 (mmol/L) using LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
Baseline value	**n**	9	7	29
	Mean (SD)	11.4 (6.03)	8.0 (2.83)	8.5 (3.45)
Month 12 value, LOCF	**n**	6	7	27
	Mean (SD)	10.2 (7.58)	6.9 (2.16)	8.3 (2.99)
Effect size: actual change from BL	**n**	6	7	27
	Mean (SD)	-1.5 (9.90)	-1.1 (2.95)	-0.2 (4.14)
	95% CI	-11.9, 8.8	-3.8, 1.6	-1.8, 1.5
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.719	0.358	0.838
Effect size: percent change from baseline	**n**	6	7	27
	Mean (SD)	-7.3 (53.71)	-9.0 (26.45)	13.9 (69.14)
	95% CI	-63.6, 49.1	-33.4, 15.5	-13.4, 41.3
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.754	0.403	0.304
Key secondary endpoint: Responder analysis: patients who met target reductions in HbA1c or triglycerides at Month 12/LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
≥1% actual decrease in HbA1c or ≥30% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	3/6 (50.0)	2/7 (28.6)	9/26 (34.6)
	95% CI[b]	11.8, 88.2	3.7, 71.0	17.2, 55.7
≥1.5% actual decrease in HbA1c or ≥35% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	3/6 (50.0)	2/7 (28.6)	9/26 (34.6)
	95% CI[b]	11.8, 88.2	3.7, 71.0	17.2, 55.7

≥2% actual decrease in HbA1c or ≥40% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	3/6 (50.0)	1/7 (14.3)	7/26 (26.9)
	95% CI[b]	11.8, 88.2	0.4, 57.9	11.6, 47.8
Other secondary endpoints: Change from baseline to Month 12 in liver transaminase levels (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
ALT (U/L)				
Baseline	**n**	9	7	29
	Mean (SD)	122.1 (140.47)	35.3 (16.64)	40.7 (34.37)
Actual change from **baseline**	**n**	4	5	19
	Mean (SD)	-191.5 (167.27)	-5.1 (12.94)	-7.4 (25.80)
AST (U/L)				
Baseline	**n**	9	7	29
	Mean (SD)	76.0 (72.52)	27.7 (8.98)	35.9 (28.44)
Actual change from **baseline**	**n**	4	5	19
	Mean (SD)	-104.1 (74.18)	-0.3 (7.21)	-3.6 (24.81)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FAS, full analysis set; GL, generalised lipodystrophy; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; PL, partial lipodystrophy; SD, standard deviation [a] PL subgroup = patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L [b] 95% CI based on the 2-sided exact binomial proportions				

Source: Study FHA101 CSR.(10)

9.6.1.6.1 Co-primary efficacy endpoints: effect of metreleptin on change from baseline in HbA1c and percent change from baseline in triglycerides

Among patients with GL, mean change from baseline to Month 12/LOCF for HbA1c was -1.2% and the mean percent change in triglycerides was -26.9%.(10) Among the 7 patients in the PL subgroup, mean change in HbA1c from baseline to Month 12/LOCF was -0.8% with a mean percent change in triglycerides of -8.5%. Note that the smaller decrease in triglycerides for this subgroup is likely related to a much lower baseline triglyceride level. Importantly, 5 of the 7 patients in the PL subgroup did show reductions from baseline to Month 12/LOCF in triglycerides ranging from -5.7% to -52.3%.

9.6.1.7 Key secondary endpoints

9.6.1.7.1 Actual and percent change from baseline in fasting plasma glucose levels at Month 12

Improvement in glucose was observed in this supportive study. Among patients with GL, mean change from baseline to Month 12/LOCF in fasting glucose was -1.5 mmol/L and for patients in the PL subgroup was -1.1 mmol/L.(10)

9.6.1.7.2 Responder analyses: Patients achieving target reductions in HbA1c and triglycerides

Overall, 3 of 6 patients with GL had a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with the same number achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides at that time.(10) In the PL subgroup, 2 of 7 patients achieved a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 1 patient achieving the highest target decreases of ≥2% in HbA1c or ≥40% in triglycerides.

Other secondary endpoints of relevance

9.6.1.7.3 Analysis of change over time in HbA1c and triglycerides: persistence of efficacy

Long-term treatment with metreleptin led to reductions in HbA1c and triglycerides in patients with GL and in the PL subgroup. The overall LS mean changes in HbA1c based on the MMRM analysis for GL patients and patients in the PL subgroup showed statistically significant decreases from baseline over all analysis visits (-0.7%; p=0.047 and -0.9%; p=0.11, respectively).(10) For triglycerides, the LS mean percent changes in triglycerides were -23.3% (p=0.059) and -4.3% (p=0.703) in the GL group and PL subgroup, respectively.(10)

9.6.1.7.4 Effect of metreleptin on hepatic enzymes

As noted in **Table C17**, approximately half of patients in the GL group entered the study with elevated hepatic transaminase levels (44% with ALT >ULN and 44% with AST >ULN). In the GL group, substantial reductions in both ALT and AST occurred during treatment with metreleptin (**Table C24**).(10) Mean change in the GL group from baseline to Month 12/LOCF in ALT was -191.5 U/L; the changes were observed early with a mean change to Month 3 in GL patients of -98.3 U/L. Similar results were observed for AST with a mean change in the GL group to Month 3 of -49.7 U/L and to Month 12 of -104.1 U/L.(10)

Reductions in transaminase levels were also observed in the PL subgroup, although of lower magnitude than that in the GL group; this is likely related to lower baseline levels of ALT and AST in this group of patients (29% with ALT >ULN, and none with AST >ULN).(10) In the PL subgroup, mean changes to Month 12/LOCF in ALT and AST were -5.1 U/L and -0.3 U/L, respectively.(10)

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

The efficacy analyses in study NIH 991265/20010769 and study FHA101 were conducted on the FAS (defined as all patients who received at least 1 dose of study drug and who had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit). Use of this analysis set for changes from baseline in HbA1c and triglycerides in this population is considered conservative,

given that not all patients would be expected to have abnormal HbA1c and triglyceride levels at baseline and therefore would not be expected to have significant reductions observed.

9.7 Adverse events

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Two relevant single-arm, open-label trials were identified in the SLR. These have been described previously in Section 9.1. Please refer to Section 9.1, 9.2 and 9.3 for the methodology and results of the SLR, Section 9.4 for details of the included metreleptin trials, and Section 9.5 for a critical appraisal of each of the metreleptin trials.

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in Table C10.

9.7.2.1 Study NIH 991265/20010769

9.7.2.1.1 Patient exposure

Total patient-years of exposure for GL patients was 328.3 years.(9) In the GL group, median overall duration of treatment was 49.9 months with similar results in males and females. Median actual duration of treatment (excluding dose interruptions) was 47.2 months, indicating that recorded dose interruptions were typically not of long duration. Dose interruptions were recorded in 18 (27%) of the 66 patients with GL; median duration of the dose interruption in this group was 48 days. Median average daily dose in GL patients was 4.4 mg and, consistent with the dosing recommendations, was higher in females (4.7 mg) than males (3.0 mg). The median weighted average daily dose over the study period in GL patients was 4.4 mg or 0.093 mg/kg and was lower in males (3.0 mg; 0.057 mg/kg) than females (5.0 mg; 0.099 mg/kg).

Total patient-years of exposure for the PL subgroup was 121.3 years.(9) Median overall and actual duration of treatment with metreleptin were both 29.3 months in this subgroup of patients. The shorter median duration of treatment in the PL subgroup compared to GL patients is related to the fact that most PL patients, who, in general, have higher leptin levels, were not eligible for the study until 5 years after study start when the eligibility criteria were modified to increase eligible leptin levels. Dose interruptions were recorded in 13% of patients in the PL subgroup; median

duration of dose interruptions was 110 days. The average daily metreleptin dose administered in PL patients was higher than in GL patients. Median average daily dose in the PL subgroup was 8.1 mg and median maximum daily dose was 10.0 mg. The median weighted average daily dose over the study period in patients in the PL subgroup was 8.2 mg or 0.119 mg/kg.

9.7.2.2 Adverse events

A summary of treatment-emergent adverse events (TEAEs) is shown in **Table C25**. In the GL group, 59 (89%) of the 66 patients reported at least 1 TEAE; drug-related TEAEs were reported in 32 (49%) of these patients.(9) Compared with the GL group, the overall incidence of TEAEs was similar in the PL subgroup with 27 (87%) of the 31 patients experiencing at least 1 TEAE; the incidence of drug-related TEAEs was lower (23%).

TEAEs of severe intensity were reported in 29 (44%) of the 66 GL patients and in 13 (42%) of the 31 patients in the PL subgroup; most severe TEAEs were assessed as unrelated to study treatment.(9)

Over the 14-year study duration, treatment-emergent deaths were reported in 4 (4%) of the 107 patients, including 3 patients with GL and 1 patient in the PL subgroup.(9) TEAEs leading to death included renal failure, cardiac arrest (concurrent with pancreatitis and septic shock), progressive end-stage liver disease (chronic hepatic failure), and hypoxic-ischaemic encephalopathy. None of the deaths were assessed as drug-related.

Overall, 23 (35%) of the 66 GL patients and 7 (23%) of the 31 patients in the PL subgroup experienced at least 1 serious adverse event (SAE).(9) The types of SAEs were consistent with the underlying LD disease, and primarily included reports of abdominal pain and pancreatitis, infections, and worsening liver function. Drug-related SAEs were not common, reported in 3 GL patients, including one case of hypertension, one of respiratory distress and one case of anaplastic large-cell lymphoma. None of the patients in the PL subgroup experience a drug-related SAE.

Discontinuations due to TEAEs were reported in 5 patients with GL (8%) and 1 patient in the PL subgroup (3%). In 4 of these 6 patients, the events leading to withdrawal led to death.(9)

The majority of the commonly reported events in the GL group were consistent with the expected pharmacologic effects of metreleptin, including weight decreased, hypoglycaemia, and decreased appetite, or were gastrointestinal (GI) disorders or constitutional symptoms, including abdominal pain and headache.(9) Other commonly reported GI disorders in patients with GL included nausea and constipation. The most commonly reported drug-related TEAEs in GL patients were weight decreased (15 patients, 23%) and hypoglycaemia (8 patients, 12%).

In general, the safety profile in the PL subgroup was consistent with that observed in the overall GL group. The most common TEAEs reported in the PL subgroup were

abdominal pain, hypoglycaemia, nausea, fatigue, alopecia and constipation. The most commonly reported drug-related TEAEs in patients in the PL subgroup were hypoglycaemia and fatigue (each 3 patients, 10%).(9)

Table C25: Adverse events: study NIH 991265/20010769 (safety analysis set)

	GL (N = 66)	PL subgroup[a] (N = 31)	PL overall (N = 41)
Overall Summary			
TEAE	59 (89.4)	27 (87.1)	35 (85.4)
Drug-related TEAE	32 (48.5)	7 (22.6)	8 (19.5)
Severe TEAE	29 (43.9)	13 (41.9)	16 (39.0)
Drug-related severe TEAE	7 (10.6)	0	0
Treatment-emergent SAE	23 (34.8)	7 (22.6)	10 (24.4)
Drug-related treatment emergent SAE	3 (4.5)	0	0
TEAE leading to study drug discontinuation	5 (7.6)	1 (3.2)	1 (2.4)
On-study deaths	3 (4.5)	1 (3.2)	1 (2.4)
Most common (≥5% Incidence overall) TEAE			
Weight decreased	17 (25.8)	2 (6.5)	2 (4.9)
Abdominal pain	11 (16.7)	6 (19.4)	6 (14.6)
Hypoglycaemia	10 (15.2)	6 (19.4)	7 (17.1)
Decreased appetite	8 (12.1)	1 (3.2)	1 (2.4)
Headache	8 (12.1)	0	0
Nausea	6 (9.1)	5 (16.1)	6 (14.6)
Fatigue	6 (9.1)	3 (9.7)	3 (7.3)
Ear infection	6 (9.1)	0	0
Arthralgia	6 (9.1)	2 (6.5)	3 (7.3)
Upper respiratory tract infection	5 (7.6)	1 (3.2)	2 (4.9)
Back pain	5 (7.6)	2 (6.5)	2 (4.9)
Anxiety	5 (7.6)	0	1 (2.4)
Proteinuria	5 (7.6)	0	1 (2.4)
Ovarian cyst	5 (7.6)	0	1 (2.4)
Depression	4 (6.1)	1 (3.2)	3 (7.3)
Alopecia	3 (4.5)	3 (9.7)	3 (7.3)
Constipation	3 (4.5)	3 (9.7)	3 (7.3)
Pain in extremity	3 (4.5)	2 (6.5)	3 (7.3)

Abbreviations: GL = generalised lipodystrophy; PL = partial lipodystrophy; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

9.7.2.3 Study FHA101

9.7.2.3.1 Patient exposure

Among the 9 patients included in the GL group in this study, median overall duration of treatment was 21.3 months.(10) Total patient-years of exposure for the GL group was 11.3 years. Dose interruptions were reported in 2 GL patients; duration of the dose interruption was 1 day in 1 patient and 1 year in the other. Median average daily dose in GL patients was 3.7 mg and median maximum daily dose over the study period was 5.0 mg. The median weighted average daily dose over the study period in GL patients was 3.7 mg or 0.057 mg/kg.

Across the 7 patients in the PL subgroup, median overall duration of treatment with metreleptin was 53.1 months.(10) Total patient-years of exposure for the PL subgroup was 28.4 years. Dose interruptions were reported in 6 of these 7 patients. Median duration of dose interruptions for these 6 patients was 4.5 days. Similar to what was observed in study NIH 991265/20010769, median average daily dose in the PL subgroup was higher than that in GL patients at 8.9 mg and median maximum daily dose was 10.0 mg. The median weighted average daily dose over the study period in patients in the PL subgroup was 9.0 mg or 0.110 mg/kg.

9.7.2.3.2 Adverse events

A summary of TEAEs is shown in

In the GL group, 7 (78%) of the 9 patients reported at least 1 TEAE; drug-related TEAEs were reported in 6 (67%) of these patients.(10) All 7 patients in the PL subgroup experienced at least 1 TEAE, and TEAEs were assessed as drug-related in 6 (86%) of these 7 patients.

In 6 (67%) of the 9 patients with GL, events of severe intensity were reported. All TEAEs in the PL subgroup were mild to moderate in severity.(10) Among the PL patients not included in the PL subgroup, events of severe intensity were reported in 9 (36%) of the 25 patients.

Two (5%) of the 41 patients died during study FHA101, including one patient with GL and one with PL (not in the PL subgroup).(10) The cause of death was progression of pre-existing adenocarcinoma in one patient and loss of consciousness following a fall in her home in another. Neither of the deaths was assessed as drug-related.

Overall, 6 (67%) of the 9 GL patients experienced at least 1 SAE, none of which was assessed as related to study treatment.(10) There were no SAEs reported in patients in the PL subgroup. Ten patients with PL who were not in the PL subgroup experienced SAEs.

Discontinuations due to TEAEs were reported in the 2 patients who died and in 2 additional patients with PL (not in the PL subgroup).(10)

In general, when considering the difference in sample size, the types and incidence for commonly reported TEAEs in study FHA101 were similar to those reported in the pivotal study NIH 991265/20010769. Among the 9 patients with GL in Study FHA101, the most commonly reported TEAEs, all reported in 2 patients (22%), were hypoglycaemia, upper respiratory tract infection, abdominal pain, increased liver function tests, and ear infection.(10) For the 7 patients in the PL subgroup, the most commonly reported TEAEs were hypoglycaemia, upper respiratory tract infection, and urinary tract infection (each 3 patients, 43%), and nausea, anxiety, and sinusitis (each 2 patients, 29%). The only drug-related TEAE reported in more than 1 GL patient was hypoglycaemia (2 patients, 22%). In the PL subgroup, the only drug-related TEAEs reported in more than 1 patient were hypoglycaemia and nausea (each 2 patients, 29%).

Table C26: Adverse events: Study FHA101 (safety analysis set)

	GL (N = 9)	PL subgroup[a] (N = 7)	PL overall (N = 32)
Overall summary			
TEAE	7 (77.8)	7 (100.0)	27 (84.4)
Drug-related TEAE	6 (66.7)	6 (85.7)	22 (68.8)
Severe TEAE	6 (66.7)	0	9 (28.1)
Drug-related severe TEAE	0	0	2 (6.3)
Treatment-emergent SAE	6 (66.7)	0	10 (31.3)
Drug-related treatment emergent SAE	0	0	1 (3.1)
TEAE leading to study drug discontinuation	1 (11.1)	0	3 (9.4)
On-study deaths	1 (11.1)	0	1 (3.1)
Most common (≥5% incidence overall) TEAE (MedDRA preferred term)			
Hypoglycaemia	2 (22.2)	3 (42.9)	11 (34.4)
Upper respiratory tract infection	2 (22.2)	3 (42.9)	6 (18.8)
Urinary tract infection	1 (11.1)	3 (42.9)	6 (18.8)
Nausea	1 (11.1)	2 (28.6)	12 (37.5)
Anxiety	1 (11.1)	2 (28.6)	2 (6.3)
Sinusitis	0	2 (28.6)	2 (28.6)
Liver function test increased	2 (22.2)	1 (14.3)	1 (3.1)
Abdominal pain	2 (22.2)	1 (14.3)	5 (15.6)
Vomiting	1 (11.1)	1 (14.3)	4 (12.5)
Headache	1 (11.1)	1 (14.3)	4 (12.5)
Injection site bruising	1 (11.1)	1 (14.3)	4 (12.5)
Lymphadenopathy	1 (11.1)	1 (14.3)	3 (9.4)
Dizziness	0	1 (14.3)	3 (9.4)
Muscle spasms	0	1 (14.3)	6 (18.8)

	GL (N = 9)	PL subgroup[a] (N = 7)	PL overall (N = 32)
Myalgia	0	1 (14.3)	3 (9.4)
Viral infection	0	1 (14.3)	3 (9.4)
Ear infection	2 (22.2)	0	1 (3.1)
Dyspnoea	1 (11.1)	0	2 (6.3)
Vertigo	0	0	4 (12.5)
Injection site pruritus	0	0	3 (9.4)

Abbreviations: GL = generalised lipodystrophy; PL = partial lipodystrophy; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] PL subgroup = PL subgroup = patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

9.7.2.4 Pooled safety analysis

In order to support the proposed product information for the marketing authorisation application (MAA) to the EMA, data were pooled across studies and LD type.(86) Table C27 provides an overall summary of all adverse drug reactions reported in patients with GL (n=75) and patients in the PL subgroup (n=38) who were treated in the two LD studies NIH 991265/20010769 and FHA101. The only events reported in >10% of these 113 patients were weight decreased (15%) and hypoglycaemia (13%); fatigue was reported in 7% of patients and injection site reaction, neutralising antibodies, decreased appetite, nausea, and alopecia were each reported in 4% of patients with all other adverse drug reactions reported in 1 (<1%) or 2 (2%) of the 113 patients.(86)

Table C27: Metreleptin Adverse Drug Reactions in all patients with GL and patients in the PL subgroup across study NIH 991265/20010769 and study FHA101 (Safety Population)

MedDRA SOC Preferred term	All GL patients AND patients in the PL subgroup (N = 113) N (%)
General disorders and administration site conditions	21 (18.6)
Fatigue	8 (7.1)
Injection site reaction	4 (3.5)
Injection site bruising	2 (1.8)
Injection site erythema	2 (1.8)
Injection site urticaria	2 (1.8)
Chest pain	1 (0.9)
Injection site induration	1 (0.9)
Injection site inflammation	1 (0.9)
Injection site pain	1 (0.9)
Investigations	21 (18.6)
Weight decreased	17 (15.0)

MedDRA SOC Preferred term	All GL patients AND patients in the PL subgroup (N = 113) N (%)
Neutralising antibodies	4 (3.5)
Liver function test increased	1 (0.9)
Metabolism and nutrition disorders	19 (16.8)
Hypoglycaemia	15 (13.3)
Decreased appetite	4 (3.5)
Gastrointestinal disorders	7 (6.2)
Nausea	4 (3.5)
Abdominal pain	2 (1.8)
Anal incontinence	1 (0.9)
Dyspepsia	1 (0.9)
Vomiting	1 (0.9)
Skin and subcutaneous tissue disorders	5 (4.4)
Alopecia	4 (3.5)
Night sweats	1 (0.9)
Nervous system disorders	3 (2.7)
Headache	2 (1.8)
Disturbance in attention	1 (0.9)
Dizziness	1 (0.9)
Reproductive system and breast disorders	3 (2.7)
Menorrhagia	2 (1.8)
Vaginal haemorrhage	1 (0.9)
Blood and lymphatic system disorders	1 (0.9)
Iron deficiency anaemia	1 (0.9)
Cardiac disorders	1 (0.9)
Tachycardia	1 (0.9)
Musculoskeletal and connective tissue disorders	1 (0.9)
Arthralgia	1 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9)
Anaplastic large-cell lymphoma	1 (0.9)
Renal and urinary disorders	1 (0.9)
Urinary incontinence	1 (0.9)
Respiratory, thoracic and mediastinal disorders	1 (0.9)
Respiratory distress	1 (0.9)
Vascular disorders	1 (0.9)
Hypertension	1 (0.9)
Abbreviations: GL = generalised lipodystrophy; MedDRA = Medical Dictionary for Regulatory Activities; PL = partial lipodystrophy; SOC = system organ class	

Source: Data on file.(86)

9.7.2.5 Selected adverse reactions

Pancreatitis

One of the primary metabolic abnormalities in patients with LD is severe hypertriglyceridaemia, which can result in life-threatening bouts of acute pancreatitis. In study NIH 991265/20010769, where medical history was more consistently reported, 31% of patients (33 of 107) reported a history of pancreatitis.(9)

Across the 148 patients included in LD studies, 6 (4%) patients (4 with GL and 2 with PL), experienced treatment-emergent pancreatitis.(1, 9, 10) All patients had a history of pancreatitis and hypertriglyceridaemia.(1, 9, 10) One of the patients who developed septic shock concurrent with pancreatitis died; the other 5 patients recovered and continued on treatment.(1, 9, 10) Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients.(1) The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridaemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridaemia.(1)

Serious infections

A significant number of patients with acquired forms of LD have low C3 levels and the presence of polyclonal immunoglobulin C3 nephritic factor, increasing the risk for recurrent bacterial infections.(22, 87)

A review of available literature was undertaken to understand the propensity as well as the rate of development of serious infection in patients with LD. The conclusion of this review was that the natural history of patients with LD with low leptin levels is to experience higher rates of infection than the general population.(5, 88-91)

In study NIH 991265/20010769, serious infections were reported in 7 (11%) of 66 patients with GL and in 2 (7%) of 31 patients in the PL subgroup.(9) The only serious infections reported in more than 1 patient in the GL group were sepsis and pneumonia, each reported in 2 patients (3%). In the PL subgroup, serious infections included cellulitis, streptococcal infection, and pharyngitis in 1 patient and osteomyelitis and cellulitis in the other. All serious infections were assessed as unrelated to study treatment and none led to treatment discontinuation. In study FHA101, no serious infections were reported in the GL group or in the PL subgroup.(10)

Hypoglycaemia

Metreleptin may decrease insulin resistance in diabetic patients, resulting in hypoglycaemia in patients with LD and co-existing diabetes.(1) Hypoglycaemia, deemed as related to metreleptin treatment, occurred in 13.3% of patients studied.

All reports of hypoglycaemia in patients with GL and in the PL subgroup, have been mild in nature with no pattern of onset or clinical sequelae.(1) Generally the majority of events could be managed by food intake with only relatively few modifications of anti-diabetic medicine dosage occurring.(1)

T-cell lymphoma

Three cases of T-cell lymphoma have been reported while taking metreleptin in clinical studies.(1) All three patients had acquired GL. Two of these patients were diagnosed with peripheral T-cell lymphoma while receiving the medicinal product. Both had immunodeficiency and significant haematological abnormalities including severe bone marrow abnormalities before the start of metreleptin treatment. A separate case of anaplastic large cell lymphoma was reported in a paediatric patient receiving the medicinal product who did not have haematological abnormalities before treatment.

Immunogenicity (neutralising antibodies)

In clinical trials (studies NIH 991265/20010769 and FHA101), the rates of antidrug antibodies (ADAs) for GL patients and the PL subgroup patients were 96% (51 out of 53 patients) and 93% (27 out of 29 patients), respectively.(1)

Overall, in patients where antibody data was available, neutralising ADA activity was observed in 38/102 patients (37%): 25/53 (47%) with GL and 6/29 patients (21%) within the PL subgroup. An attenuation (typically denoted by initial improvement and then decline of both HbA1c and triglyceride levels) and worsening (denoted by decline from baseline in both HbA1C and triglycerides) of metreleptin effect was reported in patients with PL and GL, both with and without neutralising ADAs. In the majority of patients with neutralising activity and apparent attenuation or worsening of metreleptin effect, this effect was transient and without clinical impact.

Serious and/or severe infections that were temporally associated with neutralising activity occurred in 5 GL patients.(1) These events included one episode in one patient of serious and severe appendicitis, two episodes in patients of serious and severe pneumonia, a single episode of serious and severe sepsis and non-serious severe gingivitis in one patient and six episodes of serious and severe sepsis or bacteraemia and one episode of non-serious severe ear infection in one patient. One serious and severe infection of appendicitis was temporally associated with neutralising activity in a patient with PL who was not in the PL subgroup (i.e. not the indicated population but with a similar safety profile). None of these temporally associated infections were considered related to metreleptin treatment by the study investigators. LD patients with neutralising antibodies and concurrent infections responded to standard of care treatment.

Of the 38 patients with neutralising activity

58% achieved resolution of neutralising antibodies, including 15 patients with GL and 7 patients with PL, and

87% (33/38) received uninterrupted metreleptin dosing throughout the period of neutralising activity.(1)

Injection site reactions

Injection site reactions were reported in 3.5% of patients with LD treated with metreleptin.(1) All events reported in clinical studies in patients with LD have been mild or moderate in severity and none have led to treatment discontinuation. Most events occurred during the initial 1-2 months of initiation of metreleptin.

All events reported in clinical studies in patients with LD have been mild or moderate in severity and none have led to treatment discontinuation.

9.7.2.6 Paediatric population

Across the two completed clinical studies (NIH 991265/20010769 and FHA101), there were 50 paediatric subjects (5 in the PL subgroup and 45 with GL) enrolled and exposed to metreleptin. Limited clinical data exists in children less than 6 years old.(1)

Overall, the safety and tolerability of metreleptin are similar in children and adults.(1) In GL patients, the overall incidence of drug-related adverse reactions was similar regardless of age. SAEs were reported in 15 paediatric patients, primarily reports of abdominal pain and pancreatitis (each 3 patients), and pneumonia and liver disorder (each 2 patients).(1) The only common TEAEs reported at a higher incidence (≥10% difference) in patients ≥6 to <18 years compared to adults were abdominal pain (25% vs 5%) and nausea (15% vs 0%).(1) In PL patients, assessment across age groups is limited, due to the small sample size.(1) However, there were no apparent differences in the overall incidence or the incidence of common adverse events between age categories.(1)

9.7.2.7 Provide a brief overview of the safety of the technology in relation to the scope.

The safety profile of metreleptin in patients with LD is consistent with that of a patient population with significant co-morbidities. The long-term exposure available from clinical trials across a relatively large population of patients with this ultra-rare disease provides guidance on the expected safety profile of this agent intended for chronic therapy in patients with GL and in a subgroup of patients with PL who have more significant baseline metabolic disturbances of HbA1c ≥6.5% and triglycerides ≥5.65 mmol/L.

Further, data from the post-marketing period from 138 patients who have been exposed worldwide to commercially available metreleptin (including 116 in the US

and 22 in Japan) has shown a safety profile that is consistent with that observed in clinical trials with no new safety signals identified. The identified risks of hypersensitivity, acute pancreatitis associated with metreleptin discontinuation, and hypoglycaemia with concomitant use of insulin and insulin secretagogues can be managed with risk communication in labelling and educational activities.(1, 9, 10)

In conclusion, the known side effects of metreleptin can be managed as part of the normal clinical practice for patients with this complex condition.

9.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Non-applicable.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

An evidence synthesis and/or meta-analysis were not considered appropriate. There is a lack of relevant active comparators, and current treatment for LD is supportive care, with the choice of care based on the patients' status and symptoms; therefore no indirect comparisons were conducted. See Section 9.9.1.1 for a qualitative summary of the principal findings of the metreleptin clinical studies (Study NIH 991265/20010769 and Study FHA101) and Section 9.5 for the critical appraisal of the studies.

9.9 Interpretation of clinical evidence

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

9.9.1.1 Summary of principal findings

The main benefits of metreleptin treatment in patients with GL and in the subgroup of patients with PL who have clinically similar metabolic disturbances as patients with GL can be summarised as follows:

- Clinically meaningful and statistically significant improvements in HbA1c consistent with improvement in insulin sensitivity:

    - In study NIH 991265/20010769, mean actual change in HbA1c to Month 12/LOCF was -2.2% ($p<0.001$) for GL patients and -0.9% ($p<0.001$) for patients in the PL subgroup.

    - In study FHA101, mean actual change from baseline to Month 12/LOCF for HbA1c was -1.2% for GL patients and -0.8% for patients in the PL subgroup.

- Clinically meaningful and statistically significant improvements in hypertriglyceridaemia:

    - In study NIH 991265/20010769, mean percent change in triglycerides to Month 12/LOCF was -32.1% ($p=0.001$) for the GL group and -37.4% ($p<0.001$) in the PL subgroup excluding the 1 outlying noncompliant patient.

    - In study FHA101, mean percent change from baseline to Month 12/LOCF for triglycerides was similar in the GL group as -26.9%; however, for the PL subgroup, the mean percent change was lower at -8.5% likely related to a much lower baseline triglyceride level in this group of patients. Importantly, 5 of the 7 patients in the PL subgroup in this study showed reductions from baseline to Month 12/LOCF in triglycerides ranging from -5.7% to -52.3%.

Not all patients in the studies had both raised HbA1c and triglycerides at baseline. The effect of metreleptin was even more pronounced in those patients with an HbA1c >7% or those with triglycerides over 5.65 mmol/L at baseline.

- In study NIH 991265/20010769, among 45 patients with GL who had a baseline HbA1c of 7% or greater and data available at Month 12, the mean (SD) baseline HbA1c was 9.6% (1.63) and the mean reduction in HbA1c at Month 12 was 2.8%. Among 24 patients with GL who had a baseline triglyceride level 5.65 mml/l or greater and data available at Month 12, the mean (SD) baseline triglyceride level was 31.7 mmol/l (33.68) and the mean percent reduction in triglycerides at Month 12 was 72%. Among 15 patients in the subgroup with PL who had a baseline triglyceride level 5.65 mmol/l or greater and data available at Month 12, the mean (SD) baseline triglyceride level was 27.6 mmol/l (32.88) and the mean percent reduction in triglycerides at Month 12 was 53.7%.

Clinically meaningful and statistically significant reductions in HbA1c and triglycerides were sustained over long-term treatment in patients with GL and in the PL subgroup. Most patients received 2 or more years of therapy with a maximum duration of 14 years; total patient-years of exposure across the LD studies was >500 years. Based on the results of the MMRM analysis, which takes into account changes over all visits, statistically significant reductions from baseline were observed in both HbA1c

and triglycerides in patients with GL and in the PL subgroup in study NIH 991265/20010769. Results for the MMRM analysis were directionally consistent but not statistically significant in study FHA101.

- Target responses of ≥1% in HbA1c and/or ≥30% in triglycerides were observed in patients with GL and in the PL subgroup.
    - In study NIH 991265/20010769, nearly 80% of GL patients and 68% of patients in the PL subgroup had a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 66% and 43%, respectively, achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides.
    - Patients in the supportive study also achieved these target decreases with 3 of 6 GL (50.0%) patients and 2 of 7 (28.6%) patients in the PL subgroup having a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF.
- Clinically meaningful improvements were observed in elevated hepatic enzymes and hepatomegaly, commonly used surrogate measures of hepatic steatosis.
    - Substantial improvements were observed in liver function tests in GL patients during metreleptin treatment. Reductions in transaminase levels were also observed in the PL subgroup, although of lower magnitude, likely related to lower baseline levels of ALT and AST in this group of patients.
    - Reductions in liver volume of ≥30% were observed in most patients with hepatomegaly at baseline who had post-baseline assessment, including paediatric patients.
    - These results are consistent with results published by the NIH investigators showing improvement in liver fat with metreleptin treatment assessed by MRI and/or nuclear magnetic resonance spectroscopy and in improvements in liver biopsy results in subsets of the patients studied herein by Javor et al 2005; Petersen et al 2002 and Safar-Zadeh et al 2013.(57, 58, 64)
- Improvements in insulin resistance and hypertriglyceridaemia were substantial enough that some patients were able to discontinue use of insulin, oral antidiabetic medications and/or lipid-lowering therapies.
- Effects to improve hyperphagia have been described in patients treated at the NIH by McDuffie et al 2004 and Moran et al 2004.(54, 55) Improvement in hyperphagia due to relative leptin deficiency helps to break the cycle of excess

food consumption that further exacerbates metabolic abnormalities as ingested fats are directed towards ectopic locations.

Long-term follow-up data of metreleptin treatment in LD patients over several years indicate an overall favourable safety profile. Adverse events are generally consistent with that of a patient population with significant co-morbidities. The identified risks of hypersensitivity, acute pancreatitis associated with metreleptin discontinuation, and hypoglycaemia with concomitant use of insulin and insulin secretagogues can be managed with risk communication in labeling and educational activities.

In conclusion, the majority of LD patients with metabolic abnormalities including diabetes and/or hypertriglyceridaemia who are treated with metreleptin can expect clinically meaningful (and in some instances substantial) improvements in glycaemic control and/or triglycerides levels. Even in patients who may not achieve commonly accepted treatment targets with metreleptin, improvements in metabolic abnormalities that are otherwise sub-optimally controlled with currently available therapies can be clinically meaningful, e.g decreasing triglycerides to levels that decrease the risk of acute pancreatitis and cardiovascular events and improvement in insulin-resistance leading to a reduction in the known effects of prolonged diabetes. These benefits are particularly notable in light of the marginal effectiveness of standard, currently available diabetes and lipid-lowering therapies in patients with LD due to the underlying pathophysiology and severity of the metabolic abnormalities. In addition, improvement in liver function tests and liver volume has also been observed with metreleptin treatment.

9.9.1.2 Number needed to treat (NNT) and number needed to harm (NNH)

It was not possible to estimate numbers needed to treat from the clinical trial data as there are no studies which compared treatment with metreleptin to no treatment/placebo. However, it is worth noting with respect to the NNT that in study NIH 991265/20010769, nearly 80% of GL patients and 68% of patients in the PL subgroup had a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 66% and 43%, respectively, achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides. In addition, with respect to NNH, very few patients discontinued due to a TEAE (study NIH 991265/20010769: GL patients=5 [7.6%]; PL subgroup= 1 [3.2%]; PL patients overall=1 [2.4%]; study FHA101: GL patients=1 [11.1%]; PL subgroup=0; PL patients overall=3 [9.4%]).

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Metreleptin has been evaluated in a comprehensive clinical trial programme in LD patients, which has included a large number of patients (especially in the context of this extremely rare disease) across the different LD types, including 75 patients with GL, 73 with PL and 38 in the PL subgroup corresponding to the original proposed indicated population (186 patients overall). Furthermore, treatment was continued long-term thus providing prolonged exposure to metreleptin for assessment of efficacy and safety. Over 85% of the 107 patients in study NIH 991265/20010769

received >1 year of metreleptin, 72% received >2 years, 54% received >3 years, and 28% received 6 or more years of metreleptin in this study. The maximum duration of therapy was 14 years. In study FHA101, 70% of the 40 patients with data available for exposure received >1 year, 45% received >2 years, and 35% receiving 3 years or more of metreleptin. The maximum duration of metreleptin was approximately 5.5 years. Collectively across these 2 studies in patients with LD, the total patient-years of exposure to metreleptin was 563.5 years.

A limitation was the lack of a placebo control, which precluded quantification of the true magnitude of treatment effect (i.e the magnitude of improvement in HbA1c and serum triglycerides after accounting for potential placebo effects or other confounders). However, given the rarity of the disease and the lack of therapeutic options specific for the treatment of LD, the single-arm, open-label design was considered appropriate. Moreover, because patients with LD are at risk for serious, life-threatening metabolic complications, and because marked improvements with metreleptin were demonstrated in the pilot study, utilising a placebo control in this overall patient population was considered not ethically justifiable. The study's efficacy endpoints were objective measurements, including the co-primary endpoints of HbA1c and triglycerides. These measurements were primarily obtained at a single laboratory in the pivotal study and thus treatment effects could be appropriately evaluated with a single-arm, baseline-controlled, within patient design. Further, the open-label study design afforded the greatest sample population exposure to metreleptin in this rare disease. Furthermore, given the robust responses and the duration of metabolic improvements observed with metreleptin treatment, the likelihood that the improvements occurred solely as part of the natural history of the condition or by chance alone is highly improbable.

Finally, the clinical trials did not collect data on the impact of metreleptin on the HRQoL of patients and carers, which would have been useful to explore.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The evidence base for metreleptin addresses the scope, except that study NIH 991265/20010769 and Study FHA101 did not collect data on some of the outcomes including: organ abnormality including heart and kidneys; reproductive dysfunction and HRQoL (for patients and carers; including effects on appearance). The patient population was relevant to original sought after indication, and included patients with GL and the subgroup of patients with PL with more severe metabolic complications. However, criteria for the selection of the PL subgroup is likely to change prior to approval and is currently under discussion.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

Patients with LD were enrolled in study NIH 991265/20010769 based on having at least 1 of 3 metabolic abnormalities including diabetes mellitus, fasting insulin concentration >30 µU/mL, and/or fasting triglyceride concentration >2.26 mmol/L or

postprandially elevated triglycerides >5.65 mmol/L when fasting was clinically not indicated (e.g., in infants); these are the hallmark of this syndrome, i.e., insulin resistance with diabetes mellitus and hypertriglyceridaemia. In the supportive study FHA101, patients had to be diagnosed with diabetes mellitus and/or hypertriglyceridaemia. The study populations have external validity because they appropriately represent the population of patients with LD, based on the phenotype of LD that would be expected to receive metreleptin in clinical practice. Data were presented for the PL subgroup, which reflects the original sought indication of PL patients. However, as discussed the criteria for the PL subgroup is likely to change in the final indication.

The patients in the clinical trials may have been more severe than those seen in clinical practice in England, as they were referred to a tertiary care center. In addition, they had to travel long distances to get there were possibly monitored less frequently as a result. Data from an interim analysis from the EAP, including patients in England, is expected in Q1/Q2 2018. It is possible that improvements with metreleptin may be greater if treatment is initiated earlier and patients are more closely monitored.

Various ages (covering both adult and paediatric populations) and LD types (CGL, AGL, FPL and APL) were represented in study NIH 991265/20010769 (Section 0). In clinical practise, as in the clinical studies, the subtype is related to the age of onset, with signs and symptoms generally occurring earlier in GL vs PL; and generally earlier in congenital/familial vs acquired. This is reflected in the median age of patients in the studies: in study NIH 991265/20010769 the median age of the GL group was 15 years with 68% of patients <18 years of age; patients in the PL subgroup were older (median age 38 years) compared with patients in the GL group, with 84% ≥18 years of age. In study FHA101, most patients in both groups were ≥18 years of age at the time of enrolment.

A large proportion of patients were Caucasian (Study NIH 991265/20010769: GL=47%; PL subgroup=84%; Study FHA101: GL=89%; PL subgroup=71.4%), reflecting the demographics in England. There was a predominance of female patients, which reflects the fact that females are more commonly affected in acquired lipodystrophy. A proportion of patients (20% of GL patients and 7% of PL patients) in study NIH 991265/20010769 were enrolled from Europe/Eastern Mediterranean counties, including the UK.

Patients with LD have multiple co-morbidities related to the underlying metabolic abnormalities. Consistent with this, all 107 patients in study NIH 991265/20010769 had at least one medical history event reported, including hypertriglyceridaemia, diabetes mellitus, hepatomegaly/ hepatosplenomegaly, NASH/steatohepatitis, proteinuria, pancreatitis, and hepatic steatosis (Section 0). The majority of patients were receiving antidiabetic and lipid lowering medications at study entry. This is expected to reflect patients in clinical practice.(19)

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

The criteria to select patients will be in line with the final indication in GL patients and the PL subgroup of patients with severe metabolic abnormalities. Clinicians at Addenbrooke's will determine the clinical need for metreleptin in patients who are not controlled on standard symptomatic care

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

In lipodystrophy patients, the ability to store fat is impaired, leading to excessive fat in the blood. The way in which adipose tissue—e.g., location and extent of fat loss—is impaired differs between GL and PL, as well as between phenotypes (e.g., congenital, acquired, familial). The onset of illness is childhood or adolescence, leading to progressive morbidities in adulthood (Section 6).

Fat deposits can occur in a number of organs, with significant abnormalities observed in the heart, kidney, liver and pancreas (Sections 6.1.1 and 6.1.2;

Figure B1 Figure B2). The impact of lipodystrophy is progressive, uncontrolled metabolic disease, with severe insulin resistance, early-onset diabetes, and hypertriglyceridemia. Lipodystrophy is associated with a number of other complications such as hyperphagia, dyslipidaemia, acanthosis nigricans, reproductive dysfunction, and infection. Patients can experience early death as a consequence of lipodystrophy complications (Section 6.3 and

Table B6).

Among the many physical and psychological consequences of the disease affecting patients and families, the insatiable hunger and hyperphagia (sense of starvation) that patients with lipodystrophy typically experience every day is particularly damaging (Table C28 below; Section 7.1 and Table B8), and may be associated with: Excessive food/lipid intake, uncontrolled diabetes and hypertriglyceridemia (Section 7.1;

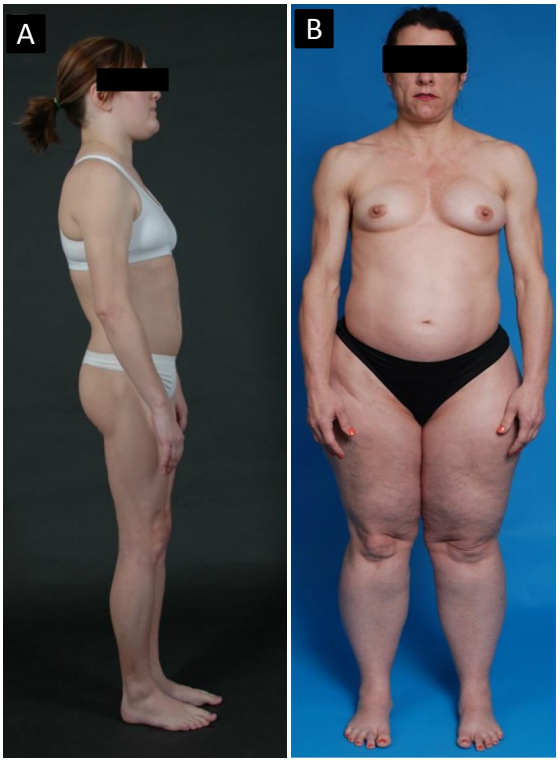
Figure B5)

- Ectopic fat deposition, organ abnormality and disease progression (Figure B2)
- Impaired or complete inability to work or attend school (Figure B8)
- Impaired physical appearance (e.g., due to disproportionate fat accumulation in body areas where adipose cells are present for PL patients) (
-
-

- Figure C20 below; Table B7)
- Depression, anxiety, and impaired quality of life (Figure B7)

An overview of lipodystrophy-related complications, clinical consequences and impact on patient quality of life can be found in Table C28.

Figure C20: The physical appearance of (A) a 26-year old female with FPL and (B) a 45-year old female with APL



Abbreviations: APL = acquired partial lipodystrophy; FPL = familial partial lipodystrophy
Source: Brown 2016 (2)

Table C28: Lipodystrophy-related complications

Complication	Clinical features	Potential impact on quality of life
Liver abnormality	• Ectopic fat deposit on liver • Hepatomegaly • Hepatic steatosis • Steatohepatitis • Cirrhosis • Liver failure	• Loss of weight and appetite • Extreme fatigue, weakness • Hallucinations, confusion or trouble concentrating • Vomiting of blood • Higher mortality risk
Heart abnormality	• Cardiomyopathy • Heart failure • Myocardial infarction • Arrhythmia	• Need for surgery • Early death • Chest pain (angina) • Need to take regular medications
Kidney abnormality	• Chronic kidney disease • Nephropathy • Kidney failure	• Need to be put on dialysis • Need for kidney transplantation • Higher mortality risk
Pancreas abnormality	• Acute pancreatitis	• Need for extra medication (e.g. diabetes, pancreatitis) • Abdominal pain • Severe pancreatitis harming other vital organs • Higher mortality risk

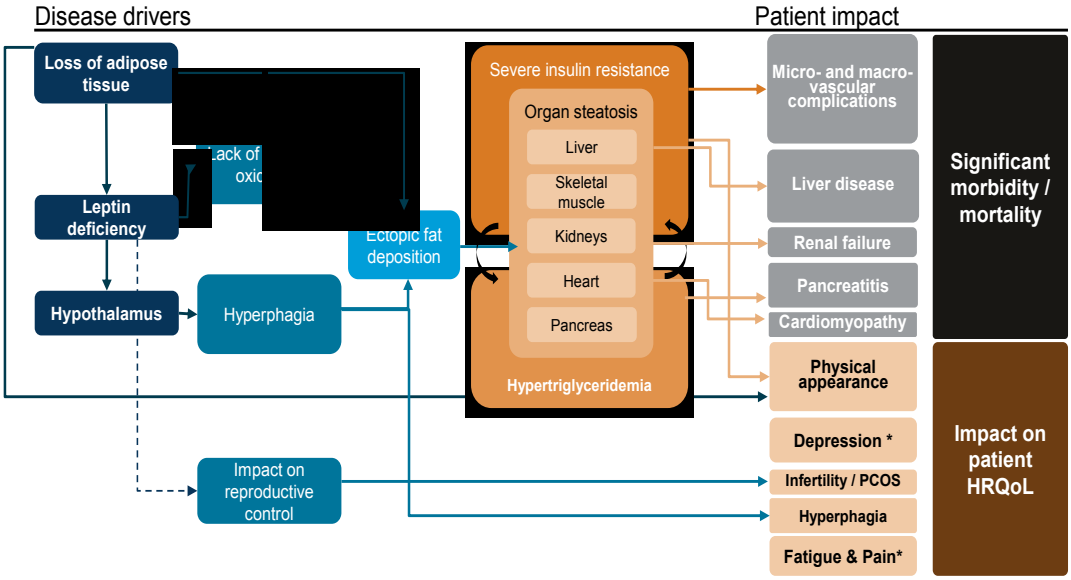
Complication	Clinical features	Potential impact on quality of life
Retinopathy	• Impairment or loss of vision due to abnormality to retina blood vessels • Typically a complication of diabetes	• Blurred vision • Blindness • Impaired social/work functioning
Neuropathy	• Peripheral nerve abnormality • Typically a complication of diabetes	• Abnormal sensation in feet and hands • Pain not easily managed with common analgesics • Impaired muscle movement
Amputation	• Common feet extremity amputations • Typically a complication of diabetes	• Impaired mobility • Grief over lost limb/depression
Impaired physical appearance	• Extreme muscularity of arms and legs • Excessive facial hair • Acanthosis nigricans • Skeletal facial features • Severe body asymmetry (swollen face vs. skinny/muscular legs)	• Low self-esteem • Depression • Need for aesthetic/restorative surgery
Female reproductive dysfunction/infertility	• Partially or completely compromised female reproductive function • Missed or irregular menstrual cycles, which can be associated with heavy bleeding • Ovarian cysts, Polycystic Ovarian Syndrome • Clitoromegaly • Ovaries produce more male hormones than normal • Physical signs (acne, male-pattern baldness, weight gain, skin tags)	• Inability to have children • Anxiety/Depression • Delayed puberty

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

Patients with congenital GL are recognised at birth or soon thereafter due to their lack of subcutaneous fat, while loss of adipose tissue in other forms typically occurs during childhood or puberty.(19) The impacts of lipodystrophy on the quality of life of patients, their caregivers and their families can be devastating. The course of GL includes progressive, uncontrolled metabolic disease, with severe insulin resistance, early-onset diabetes, and hypertriglycaeridemia. Visual damage, peripheral nerve damage, amputation and chronic pain can occur. These conditions present at an early age in GL particularly, estimated at about 2 years of age. (19) Multiple organ abnormalities (e.g., liver, heart, kidney, and pancreas) is commonly observed and the condition is characterised by early death. i.e., mean age of mortality was 12.5 years for CGL, 32.2 years for AGL, 27.8 years for FPL and 22.7 years for APL (

Table B6). A full overview of the disease course of GL and PL and their impact on patient quality of life are illustrated in Figure C21.

Figure C21: The disease course of GL and PL



HRQoL data derived from clinical trials

10.1.3 If HRQoL data were collected in the clinical trials identified in Section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation
- Method of valuation
- Point when measurements were made
- Consistency with reference case
- Appropriateness for cost-effectiveness analysis
- Results with confidence intervals.

No HRQoL data were collected in the clinical trials identified in Section 9.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D
- Details of the methodology used
- Details of validation of the mapping technique.

Since no HRQoL data were collected in the clinical trial, mapping from one instrument to another was not undertaken.

HRQoL studies

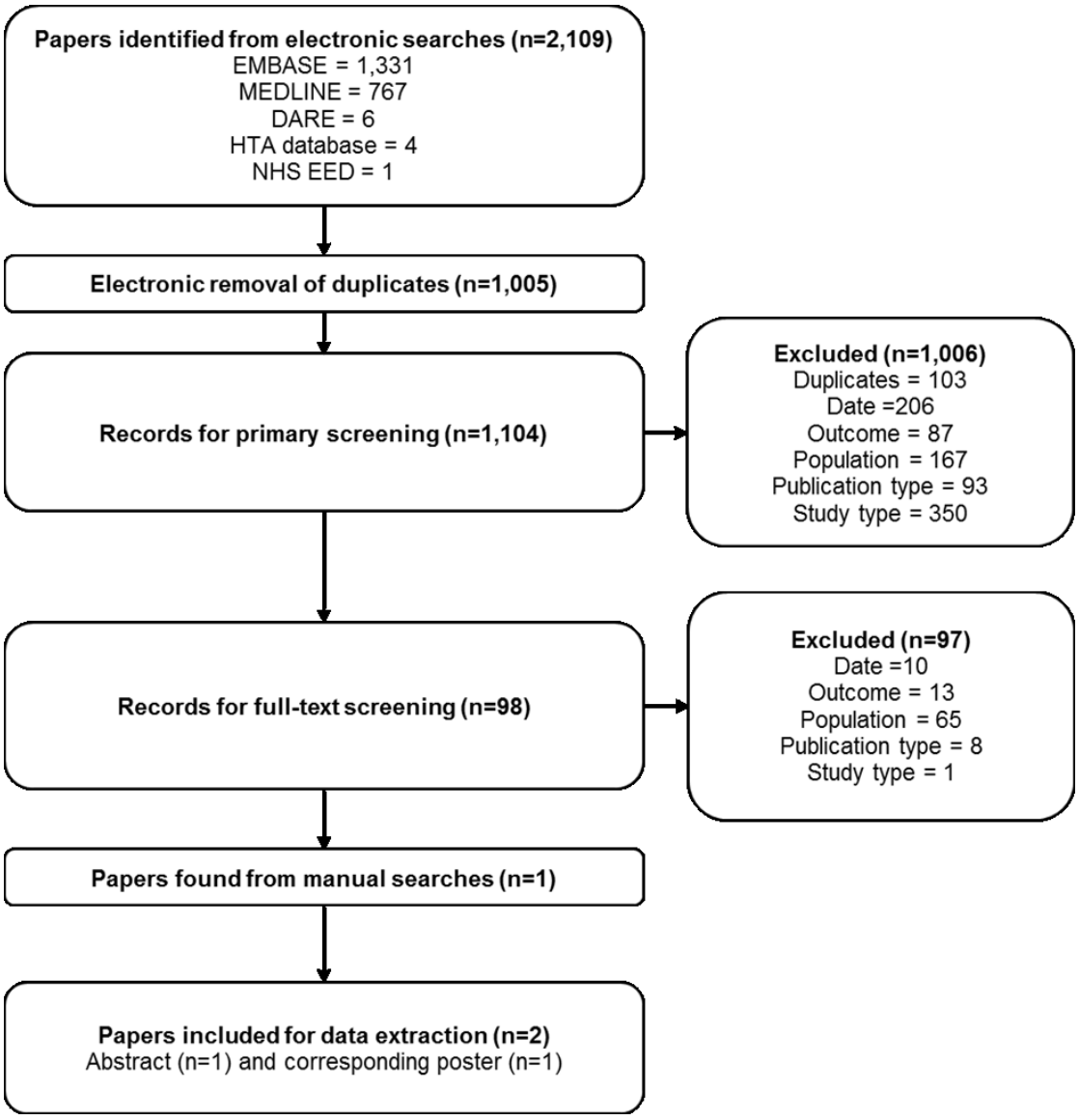
10.1.5 Please provide a systematic search of HRQoL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic review of the HRQoL data was performed in accordance with a pre-specified protocol. The aim of this review was to systematically search and identify all literature available describing the economic, cost and resource use and HRQoL evidence associated with patients with lipodystrophy.

Three separate literature searches were defined for economic, cost and resource use and HRQoL evidence. Due to the degree of overlap in search terms, the initial electronic searches were combined. After the identification of papers, screening and data extraction were independently conducted as per the inclusion and exclusion criteria defined for each review within the protocol. Individual screening processes were conducted for each of these components to increase the sensitivity and specificity of the review to address the pre-defined research objectives.

The search strategy for the combined economic, cost and resource use and HRQoL reviews is presented in the Appendix 17.3.4 Figure C22 presents results of the systematic literature searches for HRQL studies in lipodystrophy. The study selection process is detailed in a PRISMA flow chart.

Figure C22: PRISMA diagram to show the identification of HRQoL associated with lipodystrophy



Key: EED, Economic Evaluation Database; HIV, Human Immunodeficiency Virus; HTA, Health Technology Assessment; n, number; NHS, National Health Service; PRISMA, preferred reporting items for systematic reviews and meta-analyses

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.

- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Results with confidence intervals.

Two papers were identified contributing to the HRQoL evidence; one abstract and one conference poster presenting the same study: Dhankar et al. (2015). The abstract added no additional information to the conference poster, as such data extraction from the conference poster alone was performed (Table C29)

Table C29: Summary of papers identified in the HRQL review

Study	Country	Population	Cohort size, n (%)	Age (years)
Dhankar et al. (2015)	US (56%) Other (44%)	Diagnosed lipodystrophy patients OR individuals who suspect they have lipodystrophy but have not been formally diagnosed or proxies answering questions on behalf of individuals with lipodystrophy or family members of patients diagnosed with FPL or CGL	73	18-50 years: 66% 50-65 years: 30% 65+ years: 4%
Key: CGL, Congenital generalised lipodystrophy; FPL, familial partial lipodystrophy; HRQL, health related quality of life; n, number; US, United States				

Dhankar et al. (2015) evaluated the HRQoL data obtained from the participants of the Lipodystrophy Connect Registry. Patients could sign up to the registry via a website and include patients with diagnosed lipodystrophy patients, individuals who suspect they have lipodystrophy but have not been formally diagnosed, proxies answering questions on behalf of individuals with lipodystrophy or family members of patients diagnosed with FPL or CGL. 81% of patients reported having partial lipodystrophy, whereas only 4% of patients reported having generalised lipodystrophy.

Registry participants were given five surveys, including the PROMIS Global Health Short Form (SF). The PROMIS Global Health SF is a 10-item instrument representing multiple domains and could be used to calculate an EQ-5D utility score. The average estimated EQ-5D score associated with lipodystrophy was 0.67 (SD: 0.11).

The utility score was estimated based on pooled HRQoL data across all subgroups of lipodystrophy. Furthermore, the respondents were not necessarily all patients with lipodystrophy. There may be bias in the results if some of the respondents are carers of patients with lipodystrophy or if participants who wrongly think they have lipodystrophy have completed the HRQoL questionnaire. No information was provided on the clinical background of respondents.

The study was a cross-sectional study; as such, no information was provided about the impact on HRQL over time or course of treatment. Hence, due to the above limitations, this study was not considered to be useful for inclusion in the economic analysis of metreleptin reported in Section 12.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The comparison between the values derived from the literature and those reported in the clinical trials was not drawn, because no HRQoL data were collected in the clinical trials identified in Section 9.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQoL.

Hypoglycaemic events are identified as an adverse event for metreleptin across Study NIH 991265/20010769 and Study FHA101. As metreleptin lowers the effect of insulin resistance in patients with lipodystrophy with diabetes, there is an increasing risk of hypoglycaemia as the doses are titrated.

The potential impact of hypoglycaemia on HRQoL may include depression, anxiety, as well as impairment of the ability to drive, work and function.(92)The potential impact of hypoglycaemia on HRQL may include depression, anxiety, as well as impairment of the ability to drive, work and function.(92)The potential impact of hypoglycaemia on HRQoL may include depression, anxiety, as well as impairment of the ability to drive, work and function.(92)The potential impact of hypoglycaemia on HRQL may include depression, anxiety, as well as impairment of the ability to drive, work and function.(92)

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

Utility values measured by EQ-5D domains are neither available (per systematic literature review) nor fully appropriate. Dhankhar et al.(2015) (44) estimated the average EQ-5D score for lipodystrophy to be 0.67, however the domains informing the EQ-5D do not provide adequate perspective on the lipodystrophy quality-of-life burdens stemming from disease attributes such as hyperphagia, female reproductive

dysfunction, changes in physical appearance, or organ abnormality. To fill this gap, we conducted a discrete choice experiment (DCE) within the general population to provide a large-sample estimate of health disutilities associated with key lipodystrophy attributes. We surveyed 1,000 respondents in the US (250), UK (150), France (150), Germany (150), Italy (150), and Spain (150). The survey consisted of 3 components: (1) a demographic questionnaire, (2) a tutorial informing respondents of the disease and its associated attributes, and (3) a conjoint survey in which participants were asked to choose their most preferred health profile from 2 choice cards. Only participants who gave accurate responses to diagnostic questions at the end of the tutorial were allowed to proceed to the conjoint survey. Choice cards represent hypothetical patients and were constructed by assigning values to disease attributes of interest and varying these values across the 2 cards. Further details about the study methods and results are given in the Appendix 17.5.

After collecting these data, we applied standard QALY estimation techniques derived from the academic literature to generate QALY decrements associated with the relevant disease attributes (see Table C30 below). Details on how QALY decrements were estimated are given in the Appendix 17.5.

Table C30: Per-period disutility toll from lipodystrophy-related complications

State	Utility value	Confidence interval
Heart abnormality	-0.19	−0.20; −0.17
Liver abnormality	-0.15	−0.17; −0.13
Kidney abnormality	-0.13	−0.14; −0.11
Pancreas abnormality	-0.13	−0.14; −0.11
Slow progression of organ abnormality	0.03	0.01; 0.06
Fast progression of organ abnormality	-0.16	−0.18; −0.14
Unable to perform work/school work	-0.25	−0.27; −0.24
Uncontrolled constant hunger (hyperphagia)	-0.11	−0.13; −0.09
Impaired physical appearance	-0.10	−0.12; −0.08
Disruption to female reproductive functioning - Polycystic Ovary Syndrome	-0.06	−0.08; −0.03
Disruption to female reproductive functioning - Infertility	-0.17	−0.20; −0.14
Depression	-0.18	−0.19; −0.16
Chronic Pain	-0.15	−0.17; −0.13
Eye damage (Retinopathy)	-0.19	−0.21; −0.17
Nerve damage (Neuropathy)	-0.16	−0.18; −0.13
Amputation (e.g. toes, limb)	-0.27	−0.29; −0.25
Triglyceride (blood fat) control – No response or worsening	-0.11	−0.13; −0.09
Triglyceride (blood fat) control – Partial response	-0.05	−0.07; −0.03
Impaired blood sugar control – No response or worsening	-0.18	−0.20; −0.16
Impaired blood sugar control – Partial response	-0.08	−0.10; −0.06

Impaired blood sugar control – Achieved goal with hypoglycemia	-0.06	−0.08; −0.04
Increased risk of loss of response to treatment/development of neutralizing antibodies (e.g., with additional medication)	-0.15	−0.17; −0.13
Increased risk of lymphoma (a type of blood cancer)	-0.13	−0.15; −0.11

10.1.10 To validate the per-period utility decrement estimates were compared with the published literature (93) (See To validate the per-period utility decrement estimates were compared with the published literature (93) (See Figure 33 in Appendix 17.5) If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[a]:To validate the per-period utility decrement estimates were compared with the published literature (93) (See Figure 33 in Appendix 17.5) If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[b]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Leading lipodystrophy clinical experts provided input into the DCE utility survey and commented on the results. Due to the rarity of the condition, only a few clinicians are involved in the management of lipodystrophy in the UK. Three clinicians, Dr.

[b] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Rebecca Brown, Dr. David Savage, and Dr. Anna Stears, from the primary treatment centre in UK were approached and provided input based on their very extensive experience with relevant lipodystrophy patients. Dr. Brown is involved in the care of a large cohort of lipodystrophy patients at the US NIH, including participants in the metreleptin clinical trials and the observational NIH Follow-up Study. Dr. Savage and Dr. Stears practice at Cambridge University Hospital in the UK and are involved in the care of the cohort of English lipodystrophy patients treated under the existing NHS service specification (A03/S(HSS)/b) in place for insulin-resistant diabetes. A number of these patients are enrolled in the metreleptin Early Access Programme (Section 4.1).

Input from the clinicians helped identify and prioritise the lipodystrophy disease attributes included in the utility survey based on their assessment of the conditions experienced by their patients. The clinicians also reviewed and provided input on the tutorial materials used to educate survey participants on the nature of each disease attribute. There is currently ongoing work planned to review the values with the UK clinicians to investigate whether they are consistent with their experience of the relative impact of each attribute on the well being and quality of life of patients they treat in clinical practice.

10.1.11 Please define what a patient experiences in the health states in terms of HRQoL. Is it constant or does it cover potential variances?

A patient's health state is characterised by the presence or absence of a fixed set of attributes, each of which has an independent contribution to their HRQoL. Each health state yields a QALY value composed of 1 (utility from perfect health) minus the sum of the QALY decrements associated with those attributes that characterise the state (see Table C30 for the values of these QALY decrements). A starting utility value of 1 was chosen not as an accurate reflection of a hypothetical patients' true health state but rather was chosen to minimise the number of patients with negative utility values after decrements are applied. This starting utility value was chosen so that the comparison between metreleptin treatment vs SOC reflects relative differences in utility, which are reflected in the results of the economic model (Section 12.5). The QALY value of a health state is constant, in the sense that as long as the patient is in the same health state, they experience the same QALY. Table C30 also includes the 95% confidence interval of the QALY decrements generated by our analysis.

Relevant health states have not been previously characterised for lipodystrophy patients. Therefore, patient attributes are used in place of health states in cost-effectiveness modelling. In each period of the model, the individual patient attributes are different and vary from period to period.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No HRQoL data were collected in the clinical trials identified in Section 9.

The utility score estimated by Dhankar et al. (2015) (44) was not considered useful because the estimates were based on a group of respondents, which includes patients without lipodystrophy, as well as other limitations of this study (Section 10.1.6). Furthermore, there is no published literature that characterise disease attributes treated by metreleptin.

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Baseline quality of life was derived from health states that patients inhabited at the beginning of the NIH trial. For a given health state, a patient's quality of life was calculated by adding up the QALY decrements of those attributes present in that health state. Baseline quality of life for patients with no attributes present was assumed to be 1 (perfect health).

10.1.14 Please clarify whether HRQoL is assumed to be constant over time. If not, provide details of how HRQoL changes with time.

HRQoL among patients treated by metreleptin is assumed to follow real world data generated by the NIH follow-up study. This is accomplished by linking the utility decrements to the reporting of symptoms and attributes and organ damage progression in the NIH follow-up study. Because there is not direct data on HRQoL among patients treated by standard of care, most attributes are assumed to occur as they did at baseline in the NIH follow-up study and the evolution of organ damage progression (and thus associated HRQoL) is modelled as a Markov process (described in Appendix 17.6). The contribution to HRQL of those attributes that do not change over the course of a patient's life stays the same, while it decreases for those attributes (like organ abnormality) that tend to develop over the course of the patient's life.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

As part of the economic analysis a number of sensitivity/scenario analyses were conducted to explore the impact of uncertainties associated with the estimated utility decrements:

- Hyperphagia: the constant feeling of starvation associated with lipodystrophy is the quality of life impact cited as most important in numerous patient testimonials, reflecting its close relationship to the most basic of human needs. This contrasts with the results from the utility study conducted in the general public, where several other attributes were estimated as having higher impact on quality of life. Hence, the utility decrement reported in the utility study potentially lacks face validity when benchmarked against patient experiences (Section 17.5). Hence, to reflect this, a scenario analysis has been conducted in which the disutility associated with hyperphagia is increased to a value similar to that for organ abnormality (-0.22);

- Caregiver burden: data are currently not available to estimate the disutilities experienced by caregivers, particularly the families of paediatric lipodystrophy patients, who must contend with the care requirements associated with multiple comorbidities, limitations on school participation, and the challenges of managing a hyperphagic family member, who may resort to consuming non-food items and whose dietary restrictions must often be imposed on the entire household in the effort to achieve nutritional compliance in the patient. QALY impacts on caregivers from conditions which have previously been studied such as Duchenne muscular dystrophy are used in a scenario analysis. (94)

Section 12.4 describes sensitivity and scenario analyses inputs and impact on the ICER results.

Treatment continuation rules

10.1.16 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No stopping or continuation rules applied.

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

The search strategy included queries into the Embase (1974-2017 March 10); Ovid MEDLINE (1946-Present), and Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily; and the Cochrane Library, including Database of Abstracts of Reviews of Effect, Health Technology Assessment Database, and NHS Economic Evaluation Database. Key words included lipodystrophy, lawrence syndrome, Köbberling–Dunnigan syndrome, lipoatrophy, lipohypertrophy, and health economics and outcomes research analysis terms.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

Selection criteria included a human lipodystrophy population regardless of intervention; outcomes/study types related to cost effectiveness, cost utility, model structure, or budget impact; journal articles (2006 to January 2017), reports, summaries, and conference abstracts (January 2013 to January 2017). Studies were not filtered based on language. Exclusion criteria included burden of illness, HRQoL, utility-specific, cost and resource use, systematic literature, and clinical outcomes only analyses. Letters, mass media, and editorials were excluded.

Table D31: Selection criteria used for health economic studies

Inclusion Criteria	
Population	• Patients with congenital or generalised lipodystrophy • Patients with familial or partial lipodystrophy • HIV-associated lipodystrophy in which costs/HRQL were presented specific to lipodystrophy • Patients with rare lipodystrophy syndromes (e.g. Donohue syndrome, mandibuloacral dysplasia (type A and type B) and Wiedemann Rautenstrauch syndrome) • Lipodystrophy secondary to drug administration (insulin growth hormone, steroids, antibiotics and vaccinations) • Lipodystrophy secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections • Patients with lipoatrophy or lipohypertrophy if considered a subset of lipodystrophy
Interventions	• Studies were not filtered by intervention
Outcomes	• ICER (including cost per QALY, cost per life year, cost per progression free year and cost per clinical outcome), model structure, cost per benefit or budget impact of a population
Study types	• Economic evaluations including: o Cost-consequence o Cost-minimisation o Cost-effectiveness o Cost-utility o Cost-benefit o Cost-of-illness o Budget impact
Publication types	• Journal articles, reports and summaries • Papers published from 2006 (inclusive) to January 2017 • Conference abstracts published within the last four years (January 2013−January 2017, inclusive)
Other	• Studies were not filtered based on language
Exclusion criteria	
Population	• Healthy volunteers • Animal studies • Patients with HIV in which lipodystrophy was a side effect of treatment and costs/HRQL were not presented specific to lipodystrophy • Patients with lipoatrophy or lipohypertrophy specifically with no mention of lipodystrophy
Interventions	• Studies were not filtered by intervention
Study design	• Burden of illness studies • HRQL studies • Utility-specific studies • Cost and resource use analyses • Systematic literature reviews Clinical only studies (these were cross checked with studies identified in the clinical SLR)
Publication types	• Letters, newsletters, bulletins and fact sheets • Editorials or commentaries • Papers published before 2006 • Conference abstracts published before 2013

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

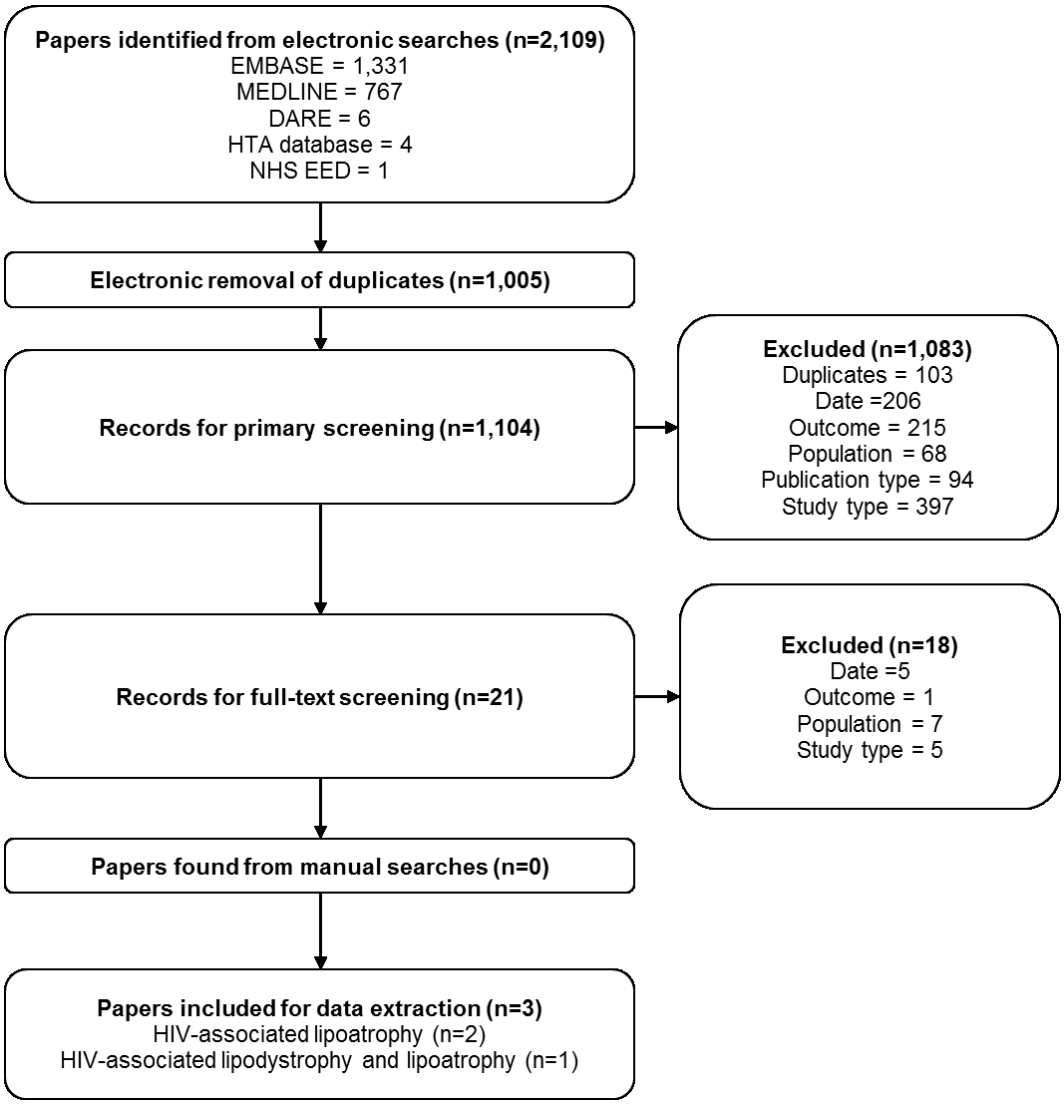
A total of 2,109 publications were identified from the electronic searches.

After removal of duplicates, 1,005 publications remained. After title and abstract screening, 1,083 publications were excluded as these were not of relevance to the research question. These papers were excluded for reasons such as study type (n=397), outcome (n=215), date (n=206), duplicates (n=103), publication type (n=94) and population (n=68).

A total of 21 articles were assessed in full for further evaluation. Of these, 18 were excluded based on population (n=7), study type (n=5), date (n=5) and outcome (n=1). This left three papers for data extraction; two papers considering HIV-associated lipoatrophy and one paper considering HIV-associated lipodystrophy and lipoatrophy.

Manual searches of key international HTA websites and disease specific conference websites identified no additional papers. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram depicting the flow of the economic review is presented in Figure D23.

Figure D23: PRISMA diagram to show the identification of economic evaluations associated with lipodystrophy



Key: EED, Economic Evaluation Database; HIV, Human Immunodeficiency Virus; HTA, Health Technology Assessment; n, number; NHS, National Health Service; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

11.2 Description of identified studies

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in Table D32.

A total of 3 studies were retrieved by the systematic literature review, none of which were relevant to economic evaluation of metreleptin. One study took place in Canada, and the other 2 took place in the United States. All 3 studies focused on patients with HIV and lipoatrophy or lipodystrophy, which are subpopulations of the indicated population for metreleptin. The studies met most of the criteria for a well-

reported, high-quality economic evaluation, but the scope of all studies was not relevant to the present submission owing to the population studied.

Table D32: Summary list of all evaluations involving costs

Study name (year and Location)	Perspective of the study and time horizon	Summary of model and comparators	Patient population (key characteristics, average age)	Costs (intervention and comparator)	Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)	Results (annual cost savings, annual savings per patient, incremental cost per QALY)
An economic evaluation of treatments for HIV-associated facial lipoatrophy: A cost-utility analysis (Peyasantiwong et al. 2010) Location: Ontario, Canada	Perspective: i) Ontario Ministry of Health. ii) Societal. Time horizon: Lifetime.	A decision tree Markov model was utilised in the cost-utility analysis of poly-l-lactic acid compared with polyalkylimide gel for the treatment of facial lipoatrophy.	Patients with HIV and facial lipoatrophy.	Direct costs and indirect costs. Costs were valued in 2009 CAD.	Incremental gain in QALYs associated with Poly-l-lactic acid and Polyalkylimide gel treatments over the patients' lifetime were 0.246 and 0.19, respectively.	ICER for Polyalkylimide gel compared with Poly-l-lactic acid (base case): i) Payer perspective: $97,907 CAD per QALY. ii) Societal perspective: $129,734 CAD per QALY. Note: Utilities gained was found to have the biggest impact on the ICER.
Economic modeling of the combined effects of HIV-disease, cholesterol and lipoatrophy based on ACTG 5142 trial data (Simpson et al. 2011) Location: United States	Perspective: US government/ third party payer. Time horizon: Lifetime.	Markov model of HIV-disease with data from ACTG 5142 study that compared LPV/r + two NRTIs with EFV + two NRTIs.	Patients with HIV and facial lipoatrophy.	Direct costs. ART drug costs were based on the AWP (Red Book). Other model costs were valued in 2007 USD.	LPV/r-based regimen vs. EFV-based regimen: 1.41 QALMs (undiscounted) gained over a lifetime.	Base case: ICER for LPV/r-based regimen compared with EFV-based regimen: $88,829 USD per QALY. Note: Scenario analyses demonstrated that changes to the lipoatrophy rates and utility decrement associated with lipoatrophy had the biggest impact on the ICER.
Lopinavir/ritonavir versus darunavir plus ritonavir for HIV infection: a cost-effectiveness analysis for the United States (Simpson et al. 2013) Location: United States	Perspective: US third-party payer. Time horizon: Lifetime.	Economic evaluation of LPV/r + TRV compared with DRV + RTV + TRV using discrete event simulation, simulating 40,000 patients over a lifetime horizon.	Patients with HIV and lipoatrophy or lipodystrophy. Mean age: 38.4 years (SD: 9.5).	Direct costs. Drug prices were based on the WAC. Other costs were obtained from claims databases specific to the US, valued in 2011 USD.	LPV/r + TRV vs. DRV + RTV + TRV Life expectancy: 27.6 vs. 27.4 years. Life-years lost because of HIV/AIDS: 14.4 vs. 14.7 years. MI rate: 9 vs. 12%.	Base case: ICER for LPV/r + TRV compared with DRV + RTV + TRV: $534,399 USD per QALY.

Abbreviations: ACTG, AIDS Clinical Trials Group; ART, anti-retroviral therapy; AWP, average wholesale price; CAD, Canadian dollar; DRV, darunavir; EFV, efavirenz; HIV, human immunodeficiency virus; ICER; incremental cost-effectiveness ratio; LPV/r, lopinavir/ritonavir; MI, myocardial infarction; NRTI, nucleoside reverse transcriptase inhibitor; QALY, quality-adjusted life year; QALM, quality-adjusted life month; RTV, ritonavir; SD, standard deviation; TRV, tenofovir and emtricitabine; US, United States; USD, United States dollar; WAC, wholesale acquisition cost.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in Table D33.

Table D33: Quality assessment of health economic studies

Lopinavir/Ritonavir Versus Darunavir Plus Ritonavir for HIV Infection: A Cost-Effectiveness Analysis for the United States		
Study design	Discrete event simulation	
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	What are the clinical outcomes and long-term economic consequences of initiating treatment of ART-naïve individuals with HIV on LPV/r over DRV + RTV?
2. Was the economic importance of the research question stated?	Yes	Drug costs are the main driver of the long-term costs of care for patients with HIV. An economic evaluation like this would inform decision makers about the downstream economic consequences of managing patients with HIV and policy decisions concerning coverage. Savings at the patient level could enable programmes with fixed budgets to serve more HIV-infected patients.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	US third-party payer perspective.
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	The model is limited to patients for whom clinicians believe that LPV/r or DRV + RTV are good options as a first-line regimen. Hence, in this economic evaluation, treatment-naïve individuals in ARTEMIS trial were modelled over a lifetime, and outcomes with first-line DRV + RTV were compared with those with LPV/r, both in combination with TRV.
5. Were the alternatives being compared clearly described?	Yes	DRV + RTV- and LPV/r-based regimens were compared in this economic evaluation and were described in ARTEMIS trial. In this trial, there were minor differences between these two regimens on viral suppression rate.
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis using a DES.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The economic evaluation aimed to predict outcomes beyond the trial (ARTEMIS), using DES. Individual patient characteristics were modelled explicitly, and these were used to predict treatment effectiveness, treatment sequencing, clinical progression and resource utilization.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Efficacy data were obtained from the ARTEMIS trial and where unavailable from other ART-naïve studies. The main efficacy outcomes were based on virological suppression and viral rebound rates. Adverse events were included based on CD4+ T-cell count.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	The ARTEMIS trial compared first-line ART with LPV/r to DRV + RTV for HIV-1-infected subjects. In this study, proportions of patient with a viral load of < 50 copies/mL were 79 % for DRV + RTV and 71 % for LPV/r at 96 weeks, the HDL/TC was slightly in favour of the LPV/r arm, and the CD4+ T-cell increases were nearly identical.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	QALYs gained and lifetime incremental costs for LPV/r regimen compared with DRV + RTV regimen.

12. Were the methods used to value health states and other benefits stated?	N/A	Utility decrements were applied for clinical events and side effects based on data in the literature. Lifetime decrements were assumed for all chronic events.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Patients with HIV and lipoatrophy or lipodystrophy.
14. Were productivity changes (if included) reported separately?	N/A	Given US third-party payer perspective, only direct costs were considered.
15. Was the relevance of productivity changes to the study question discussed?	N/A	Given US third-party payer perspective, only direct costs were considered.
16. Were quantities of resources reported separately from their unit cost?	No	Only unit costs were reported.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Drug prices were based on the WAC. Other costs were obtained from claims databases specific to the US.
18. Were currency and price data recorded?	Yes	Currency: 2011 USD.
19. Were details of price adjustments for inflation or currency conversion given?	Yes	The resource use and costs were inflated to 2011 USD using the medical care portion of the consumer price index.
20. Were details of any model used given?	Yes	A DES was developed to simulate 40,000 patients over a lifetime horizon to predict the clinical progression of treatment-naïve patients with HIV-1 infection from initiation of ART and to evaluate costs and consequences over a lifetime. The model starts by creating a population of patients with defined characteristics. Each individual is copied to provide identical populations for comparisons. These individuals are exposed to the relevant risks and experience the specific events during the simulation. These events/times, as well as patient characteristics, are updated instantaneously throughout the simulation, depending on the patient's course.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	A DES was chosen because this technique is best able to address the complex clinical and economic aspects relating to the progression of HIV infection and ART. A DES allows the time component to be handled properly and the individuals' characteristics and disease and treatment history to play out in the risk predictions.
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime horizon.
23. Was the discount rate stated?	Yes	Costs and benefits were discounted at 3% per year.
24. Was the choice of rate justified?	Yes	Standard in health economic evaluations, discounting 3−5% annually.
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Model factors subject to parameter uncertainty were varied within their confidence intervals.
27. Was the approach to sensitivity analysis described?	Yes	The uncertainty around the base model prediction was examined in a PSA. The effects of parameter and model structural assumptions on the estimates were examined by univariate and structural sensitivity analysis.
28. Was the choice of variables for sensitivity analysis justified?	Yes	Several factors were tested in sensitivity analyses which include time-dependent estimates of CD4+ T-cell count patterns, correlation between viral load and CD4+ T-cell counts, the impact of patient characteristics on viral suppression, and their impact on model outcomes was accounted for by examining their effects together in the PSA.

29. Were the ranges over which the parameters were varied stated?	Yes	In sensitivity analyses, net monetary benefit ranged from $12,808 USD to $31,357 USD, favouring LPV/r (base case $27,762 USD).
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	The incremental analysis compared LPV/r + TRV and DRV + RTV + TRV because these are good options in the first-line treatment of patients with HIV.
31. Was an incremental analysis reported?	Yes	Base case results found that the ICER for LPV/r + TRV compared with DRV + RTV + TRV was $534,399 USD per QALY (net monetary benefit of $27,762 USD).
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	The outcomes were presented as base case and as well as based on subgroups.
33. Was the answer to the study question given?	Yes	The results of this economic evaluation indicate that although similar health effects are expected for both the regimens, the initial use of LPV/r will result in lower costs. Furthermore, the use of LPV/r resulted in lower MI rates.
34. Did conclusions follow from the data reported?	Yes	The choice of first-line ART in HIV has considerable downstream economic impact. The use of an LPV/r-based regimen for ART-naive patients for whom clinicians believe that LPV/r or DRV + RTV are good options is predicted to result in cost savings that increase over time and similar health outcomes.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Several limitations: First, the assumption that the relationship between HIV RNA suppression and CD4+ T-cell count increases is used to predict clinical and survival effects. Second, existing algorithms that estimate the likelihood of various resistance mutations were not used because they are not publically available. Instead, rates of resistance mutations by drug class from clinical trials were used. Third, the choice of a salvage regimen in practice will depend on each individual patient's genotype profile. The study assumed a limited set of regimens after initial drug failure. Fourth, perhaps due to differences in definitions, estimates of side effects and treatment discontinuation rates are not consistent across trial reports. Fifth, the appropriateness of the Framingham risk model in HIV remains unclear.
36. Were generalisability issues addressed?	Yes	The study clearly defined the decision-making audience for the model (US third-party payer). The cost inputs were based on the databases specific to the US.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination. **Abbreviations:** ART, antiretroviral therapy; DES, discrete event simulation; DRV, darunavir; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; LPV/r, lopinavir/ritonavir; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; RTV, ritonavir; TC, total cholesterol; TRV; tenofovir and emtricitabine; US, United States; USD, United States dollar; WAC, wholesale acquisition cost.		
Economic modeling of the combined effects of HIV-disease, cholesterol and lipoatrophy based on ACTG 5142 trial data.		
Study design	Markov model	
Study question	Response (yes/no/not clear/N/A)	Comments
1. Was the research question stated?	Yes	What are the long-term costs and consequences of initiating an ARV regimen including LPV/r or EFV?
2. Was the economic importance of the research question stated?	Yes	The model provides information on the importance of judging clinical trial (ACTG 5142) results for ARV regimens on more

		than simply the viral load suppression at 48 weeks under ITT analytical assumptions.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Government/third-party payer perspective.
4. Was a rationale reported for the choice of the alternative interventions compared?	Yes	LPV/r-containing regimen was compared with EFV-based regimen because of their differential effects on virologic and immunologic outcomes, and lipoatrophy.
5. Were the alternatives being compared clearly described?	Yes	LPV/r-based regimen and EFV-based regimens were described in terms of virologic failure, resistance, CD4+ T-cell recovery, and effects on lipoatrophy.
6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis using Markov model.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	The economic evaluation aimed to predict outcomes beyond the trial (ACTG 5142), using Markov model. A decision-analysis modelling approach was utilized with the model inputs derived from patient-level clinical trial data to compare the expected long-term economic and HRQL consequences of initiating ART therapy with an NNRTI-based vs. a PI-based regimen for treatment- naïve patients.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Utility weights were obtained using the ACTG 5142 study data. The main efficacy measures were based on the observed CD4+ T-cell counts and the viral load values from the study. Drug prices (AWP) were obtained from the Red Book 2007. Cost data were obtained from the US Medicaid payment and hospital all-payer discharge data.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	The ACTG 5142 study was a large, randomized, phase III trial that was designed to compare the efficacy of 2 recommended first-line regimens− an NNRTI-based regimen consisting of EFV plus 2 NRTIs and a PI-based regimen consisting of LPV/r plus 2 NRTIs.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	QALYs gained and lifetime incremental costs for LPV/r -based regimen compared with EFV-based regimen.
12. Were the methods used to value health states and other benefits stated?		CD4+ T-cell counts and the HIV-1 RNA (viral load) values from the ACTG 5142 study were used to assign a specific health state to each patient for each quarter year.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Model inputs were derived from patient-level clinical trial data (ACTG 5142 study).
14. Were productivity changes (if included) reported separately?	N/A	Direct costs only − Payer perspective.
15. Was the relevance of productivity changes to the study question discussed?	N/A	Direct costs only − Payer perspective.
16. Were quantities of resources reported separately from their unit cost?	No	Unit costs were reported:
17. Were the methods for the estimation of quantities and unit costs described?		Drug prices based on the AWP were obtained from the Red Book 2007.
18. Were currency and price data recorded?	Yes	2007 USD
19. Were details of price adjustments for inflation or currency conversion given?	N/A	

20. Were details of any model used given?	Yes	A Markov model of HIV-disease was populated with patient-level clinical data (on viral load, CD4+ T-cell count, treatment-emergent resistance, treatment-emergent lipoatrophy and HRQL from the ACTG 5142 study).
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	The base model structure used in this study was used previously to estimate economic outcomes for LPV/r atazanavir, and tipranavir. The model was based on the viral load values and CD4+ T-cell counts from the ACTG 5142 study to define health states.
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime.
23. Was the discount rate stated?	Yes	Costs and outcomes were discounted by 3% annually.
24. Was the choice of rate justified?	Yes	Standard in health economic evaluations, discounting 3−5% annually.
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	The model results were not dependent on statistical tests of significance.
27. Was the approach to sensitivity analysis described?	Yes	Different assumptions and utility weights were modelled in the sensitivity analysis.
28. Was the choice of variables for sensitivity analysis justified?	Yes	When the model assumed a 50% reduction in the HRQL weight associated with lipoatrophy, the ICER increased substantially. Thus, the effect of lipoatrophy on patients' quality of life is a more important variable than the cost of treating lipoatrophy, where the ICER only increased minimally.
29. Were the ranges over which the parameters were varied stated?	Yes	In the sensitivity analysis, change in lipoatrophy QALY to "+50% and -50%" (from -0.52 in base model to -0.26 or -0.78) resulted in varying the ICER estimates for LPV/r regimen between $68,535 and $175,538.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	DHHS and other guidelines recommend the treatment of treatment-naïve HIV patients with 2 NRTIs and either a PI inhibitor, an INSTI, or a NNRTI. Hence, the model used the data from the 2 NRTI-containing arms with LPV or EFV from the ACTG 5142 study for this analysis.
31. Was an incremental analysis reported?	Yes	ICER for LPV/r-based regimen over EFV-based regimen was $88,829/QALY (base estimate).
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	The model also considered the lipoatrophy sub-population. The effects of lipoatrophy on HRQL were tested in the sub-model. When the model assumed a 50% reduction in HRQL weight associated with lipoatrophy the ICER increased from $88,829/QALY in the base model, to $175,538/QALY.
33. Was the answer to the study question given?	Yes	The costs, HRQL, adverse events, and the effect of resistance on sequential therapy interact and may affect long-term costs and consequences.
34. Did conclusions follow from the data reported?	Yes	The study demonstrated that the cost-effectiveness of ARV regimens may be strongly affected by enduring AEs, such as lipoatrophy. It is important to consider specific AEs from all drugs in a regimen when ARVs are compared.
35. Were conclusions accompanied by the appropriate caveats?	Yes	The model is limited in that CNS and gastrointestinal side effects (which can sometimes be chronic) are not included in the model. RCT results are the gold standard for defining efficacy and safety of therapy, but are limited to the relatively short duration of the study in comparison with life-long treatment currently needed for HIV- infection.
36. Were generalisability issues addressed?	Yes	The study clearly defined the decision-making audience for the model (government/third-party payer in the US). The cost inputs were based on the databases specific to the US.

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

Abbreviations: ACTG 5142, The AIDS Clinical Trials Group 5142 study; AE, adverse event; AIDS, acquired immunodeficiency syndrome; ARV, antiretroviral; AWP, average wholesale price; CNS, central nervous system; DHHS, Department of Health and Human Services; EFV, efavirenz; ENF, enfuvirtide; ETV, etravirine; HIV, human immunodeficiency virus; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; INSTI, integrase strand transfer inhibitor; ITT, intent-to-treat; LPV/r, lopinavir/ritonavir; MI, myocardial infarction; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; QALY, quality-adjusted life year; RCT, randomised controlled trial; US, United States; USD, United States dollar; VAS, visual analog scale.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 Description of the de novo cost-effectiveness analysis

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The model was developed with the data available from the NIH Follow-Up study, which includes patients with either GL or PL and a mix of paediatric and adult patients.

Some patients included in this study did not meet all characteristics of the expected licensed indication (e.g., some were younger) and thus the primary analysis is restricted to the anticipated licensed population. These patient groups include:

- patients with congenital or acquired GL, in adults and children 6 years of age and above
- patients with familial or acquired PL, characterised by leptin level < 12 ng/ml with triglycerides > 500 mmol/l and/or HbA1c > 8 %, in adults and children 12 years of age and above uncontrolled on standard therapy.

A sensitivity including all 112 patients in the NIH follow-up study is also included.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

Intervention: Metreleptin, a recombinant analogue of the human hormone leptin, administered through subcutaneous injection

Comparator: Standard clinical management without metreleptin (including lifestyle modifications such as diet and exercise, use of lipid lowering drugs; and medications for diabetes)

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

The cost-effectiveness model utilises an individual patient level modelling approach, as shown in Figure D24. All patients treated in the NIH study who meet the expected EMA labelled indication for metreleptin are included in the model (80 of 112).

The model evaluates health states of individual patients defined through a set of 13 total attributes, which serve as indicators of impairment. These attributes determine a patient's QALY value in each period. Patients are modelled for a maximum of 60 periods (years) from the start of treatment and alternative model time horizons are considered in sensitivity analysis. Individual patient health states can vary across periods when additional attributes are impaired, or when impaired attributes resolve due to treatment.

Two identical cohorts of patients ("treatment" and "standard of care") with the same baseline attributes are populated in the model at period 0 (see Table 76 for a summary of these characteristics). These attributes are obtained from the baseline health states of all patients in the NIH Follow-Up study, an ongoing observational study of 112 treated with metreleptin (see section 4.1 for a summary of the NIH Follow-Up study). Beginning in period 1, real-world data from the NIH Follow-Up study is used to populate patient-level attributes (such as the presence/absence of lipodystrophy-related complications and HbA1C/triglyceride levels) in the metreleptin treatment arm until the end of data availability for each patient. Once real-world data is no longer available for a given patient, organ abnormality progression is simulated in each subsequent period according to a specified progression rule that is explained below. The patient's other attributes are assumed to remain fixed until the end of the model time horizon.

A subset of four attributes play a crucial role in how mortality is simulated – these are abnormalities in a patient's heart, liver, kidney and pancreas. The model assumes that only impairment to these organs affects a patient's survival probability. Mortality is higher (lower) for patients with more (fewer) organs with abnormalities shown by Cox proportional hazards modelling, a regression model used for investigating association between the survival time of patients and one or more predictor variables. For instance, a patient with a heart abnormality would face a lower survival probability between the same two periods as another patient with no abnormalities. (See 17.6.2.3 for additional details) The effect of metreleptin on mortality The rate of organ abnormality progression is higher in standard of care patients than in treated patients for each possible transition (e.g., 2 organs with abnormalities to 3 organs with abnormalities), although the magnitude of the difference is more pronounced for some transitions than others. Survival probabilities in each period are determined by the number of organs with abnormalities that a patient has. In the model patients can have 0, 1, 2, 3, or 4 organs with abnormalities.

Once the observed patient data ends, the number of organs with abnormalities for metreleptin treated patients are extrapolated, following a Markov process, which in

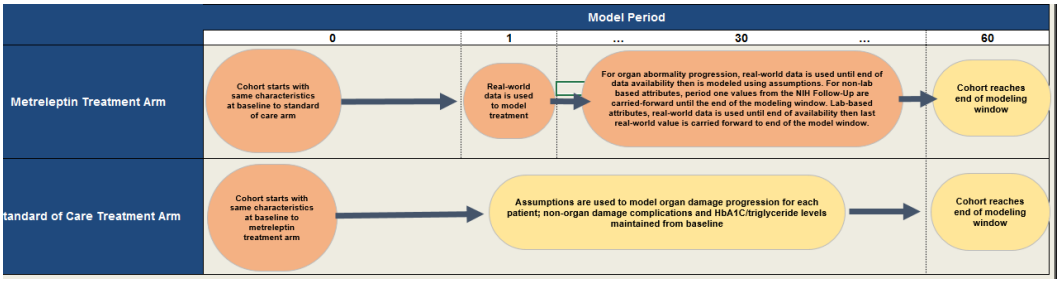
turn affects predicted mortality for each patient. Based on the number of impaired organs, expected utility and medical costs are assigned using an average across types of organ abnormalities weighted by the frequency of abnormalities associated with each organ during period when real-world data are available. While other patient or disease characteristics may influence how treatment affects mortality, the modelling approach is conservative in that potential mortality benefits are mediated only by changes in organ impairment alone, and no other excess mortality risk is assumed for patients receiving only standard of care.

For patients in the standard of care arm, organ abnormality progression is also estimated according to a Markov process, beginning in period 1 with different progression probabilities that are derived from the GL/PL natural history study. For all other attributes, these patients maintain their baseline levels of impairment throughout the model time horizon - period 0 through period 60. That is, standard of care patients are assumed to start with the same health states as the metreleptin treated patients in the NIH follow-up study, but diverge as their attributes, other than organ abnormality remain fixed at the study baseline values. The objective of this exercise is to generate a credible counter-factual trajectory for standard of care patients to capture what would have occurred to metreleptin treated patients had they never subsequently received treatment. Comparing the outcomes of patients in this counter-factual trajectory to the observed path of treated patients yields metreleptin's treatment effect.

There are two drivers of QALY gain in the model. The improved survival and consequent life years gained are associated with slower organ abnormality progression, improvements in quality of life contribute to QALY gains through reduced impact of organ abnormalities and other symptoms and attributes of lipodystrophy such as hyperphagia, impaired participation in school and work, depression, and pain. The true utility decrement associated with hyperphagia is likely understated as the DCE cannot fully encompass the patient experience of such a unique aspect of the disease [described further in Appendix 17.5].

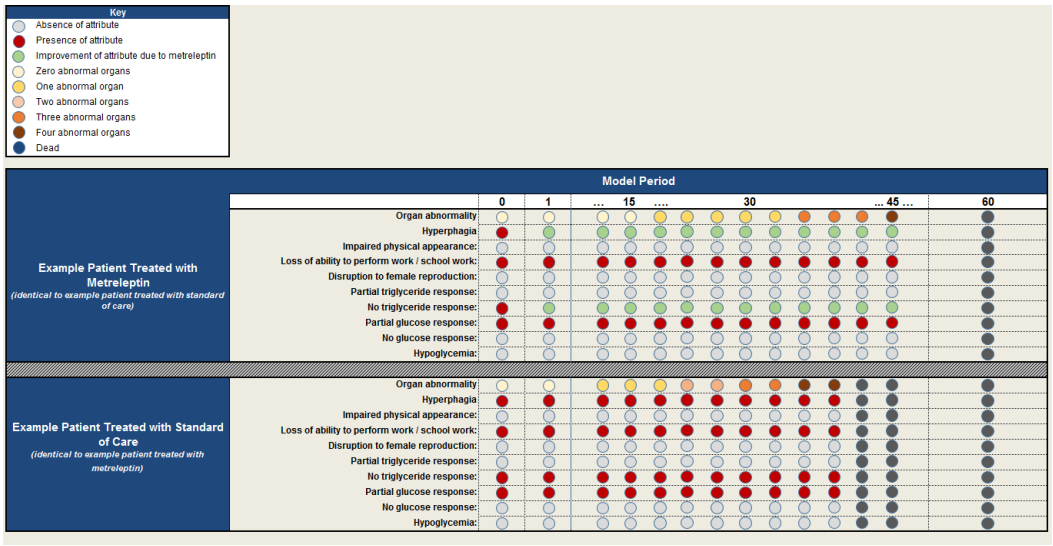
Patients' expected utility and the medical costs associated with the range of other attributes are captured by multiplying a patient's survival probability by their utility over the time horizon. Survival probabilities, QALYs, medical costs, and treatment costs are simulated for standard of care patients from period 1 through period 60 (end of modelling time horizon), and from the end of observed patient data from the NIH Follow-Up study through period 60 for treated patients.

Figure D24: Individual patient model structure



An example patient treated with metreleptin can also be represented visually in comparison to their counterpart in the standard of care treatment arm (both patients are identical at baseline), shown in Figure D25.

Figure D25: Individual sampling model structure (patient example)



12.1.4 Justify the chosen structure in line with the clinical pathway of care.

Clinical pathway of care

Lipodystrophy is a progressive, uncontrolled metabolic disease. It can cause a number of outcomes throughout a patient's lifetime. The impact of lipodystrophy can include premature mortality driven by the development and subsequent worsening of organ abnormalities. Additionally, lipodystrophy impacts patient's quality of life via female reproductive dysfunction, metabolic abnormalities, hyperphagia, pain, and depression. These conditions have the potential for interaction with a cumulative effect on patient quality of life, and they present at an early age, in GL particularly. Median age of first reported symptoms in a recent study of patients treated at the US NIH was about 8 years for GL and 17 years for PL.(9) The probability of experiencing each of these outcomes will depend on baseline characteristics, previous events, and response to therapy. Median age of first reported symptoms in a recent study of patients treated at the US NIH was about 8 years for GL and 17 years for PL.(9) The probability of experiencing each of these outcomes will depend on baseline

characteristics, previous events, and response to therapy. Median age of first reported symptoms in a recent study of patients treated at the US NIH was about 8 years for GL and 17 years for PL.(9) The probability of experiencing each of these outcomes will depend on baseline characteristics, previous events, and response to therapy. Median age of first reported symptoms in a recent study of patients treated at the US NIH was about 8 years for GL and 17 years for PL.(9) The probability of experiencing each of these outcomes will depend on baseline characteristics, previous events, and response to therapy. Median age of first reported symptoms in a recent study of patients treated at the US NIH was about 8 years for GL and 17 years for PL.(9) The probability of experiencing each of these outcomes will depend on baseline characteristics, previous events, and response to therapy.

The model structure adopted uses the actual individual patient data on characteristics and outcomes for the metreleptin treated patients and uses modelling methods to perform a comparison with SoC patients, and to extrapolate outcomes beyond the observed data. A Markov modelling structure was considered but the systematic literature review of economic studies reported in section 11 has shown that relevant health states and transition probabilities have not previously been characterised for lipodystrophy patients, in part because disease manifestation and progression is complex and implicates multiple systems. Simplifying this relatively high dimension problem into a Markov-based cohort model would provide insufficient transparency into disease status and progression, requiring aggregation of many attributes into a set of model health states that have not themselves been previously defined or studied and showing substantial homogeneity among patients. Such an approach also fails to make full use of the rich individual data on lipodystrophy patients extending as long as 15 years following initiation of treatment.

Therefore, based on a feasibility assessment of the most appropriate modelling approach for this economic analysis, an individual patient modelling approach was selected, similar to the individual sampling modelling (ISM) approach specified in the taxonomy of model structures of Brennan et al. 2016 (Table D34 and Table D35). Adopting a model structure based on individual patient data allows full utilisation of existing clinical and observational study data to account for each of the pertinent covariates and directly reflects the baseline characteristics of individual patients. (95) Adopting a model structure based on individual patient data allows full utilisation of existing clinical and observational study data to account for each of the pertinent covariates and directly reflects the baseline characteristics of individual patients. As is common with ultra-orphan conditions there is limited clinical data available for metreleptin, so the modelling approach ensures optimal use of the individual patient data that is available for estimating and extrapolating HRQoL and mortality outcomes for metreleptin relative to standard of care. Currently, the model uses individual patient data from the NIH follow-up study to estimate treatment effect, although further real world data of direct relevance to UK clinical practice is expected to become available in due course from the UK Early Access Programme at CUH, an ongoing observational study of 30 patients treated with metreleptin, 12 GL and 18 PL in the UK. When available, this can also be used in the economic model. Where individual patient data are not accessible (e.g., for model periods extending beyond

the observational data window for individual patients), a Markov-like approach is used [see description in 12.1.3 and additional details in Appendix 17.6].

The current model calculates QALY gains from treatment by following the trajectory of patients over time in a treatment and standard of care (SOC) arm of the model. The data sources used to populate the model include: two retrospective chart review studies (henceforth referred to as the NIH Follow-Up study and the GL/PL natural history study). The NIH Follow-Up study follows a cohort of patients treated with metreleptin at NIH including those enrolled in the pivotal trial. The GL/PL natural history study in an ongoing observational chart review study which collected data from over 175 lipodystrophy patients from US, Turkey and Brazil who were not treated with metreleptin (summarised in Section 4.1)

Patients in the model experience impairment with a defined probability to 13 attributes related to lipodystrophy. Each attribute level is associated with a utility decrement generated in a separate discrete choice experiment study (see section 10.1.9). Baseline attribute levels for patients in both treatment and SOC arms are based on NIH data measured at the time of enrolment. The evolution of impairment to the attributes of patients in the treatment arm uses the observed data in the NIH study for the duration of the observation period. At the end of the observation period, impairment is simulated according to a specified rule (see Section 12.2.2). Attributes of patients in the SOC arm either remain constant or evolve according to specified rules that plausibly reflect what would have occurred to treated patients had they never received the drug.

Table D34 provides details about the selection process and the justification, according to the check list provided by Brennan et al.

Table D34: Taxonomy of Model Structures

			A	B	C	D
			Cohort/Aggregate Level/Counts		Individual Level	
			Expected value, Continuous state, Deterministic	Markovian, Discrete State, Stochastic	Markovian, Discrete State, Individuals	Non-Markovian, Discrete-State, Individuals
1	**No Interaction Allowed**	**Untimed**	Decision Tree Rollback	Simulated Decision Tree (SDT)	Individual Sampling Model (ISM): Simulated Patient-Level Decision Tree (SPLDT)	
2	**No Interaction Allowed**	**Timed**	Markov Model (Evaluated Deterministically)	Simulated Markov Model (SMM)	Individual Sampling Model (ISM): Simulated Patient-Level Markov Model (SPLMM) (variations as in quadrant below for patient level models with interaction)	
3	**Interaction**	**Discrete Time**	System Dynamics (Finite Difference Equations, FDE)	Discrete Time Markov Chain Model (DTMC)	Discrete-Time Individual Event History Model (DT, IEH)	Discrete Individual Simulation (DT, DES)

4		**Continuous Time**	System Dynamics (Ordinary Differential Equations, ODE)	Continuous Time Markov Chain Model (CTMC)	Continuous Time Individual Event History Model (CT, IEH)	Discrete Event Simulation (CT, DES)

Adapted from: Brennan A, Chick S, Davies R. A Taxonomy of Model Structures for Economic Evaluation of Health Technologies. Health Econ. 2012; 15: 1295–1310 (95)

Table D35: Choice of Model Structure

	Issue	Answer for GL/PL-MET model	Example	Choice of model
I1	Does the decision maker require knowledge of variability to inform the decision?	No effect of intervention large and main variability due to patient heterogeneity (i.e., non-stochastic)	Effects of intervention are small and variable over time	Need for stochastic output (columns B to D)
I2	Is the decision maker uncertain about which sub-groups are relevant and likely to change his/her mind?	Possibly (individual-level leads to more options)	Decision maker may want to sub-divide the risk groups or test new interventions	Individual level models are more flexible to further covariates or changed assumptions (columns C and D)
I3	Is Probabilistic Sensitivity Analysis (PSA) required?	No?	Decision maker uses cost-effectiveness acceptability curves or expected value of information	Deterministic model may be preferred (column A) but need for PSA should not drive model structure decisions
I4	Do individual risk factors affect outcome in a non-linear fashion?	Yes	Effects of age, history of disease, co-morbidity	Need to subdivide states in an aggregate model. Need to consider individual level modelling if the number is large. (columns C and D)
I5	Do covariates have multiple effects, which cause interaction?	Yes	Co-morbidities in diabetes affect renal failure and retinopathy	Individual level modelling likely to be necessary. (columns C and D)
I6	Are times in states non-Markovian?	No/not clear (may depend on nature of health states being considered)	Poor survival after an operation, moving from one age group to another, length of stay in hospital	Need to use “fixes” in Markovian models or use non-Markovian models (columns D)
I7	Is the dimensionality too great for a cohort approach?	Yes	Large number of risk factors and /or subdivision of states to get over non-Markovian effects	Individual level modelling likely to be necessary. (columns C and D)
I8	Do states ‘recycle’?	Not clear	Recurrence of same illness. E.g. heart attack, stop responding to drugs	Decision tree approach is probably not appropriate (rows 2 to 4)
I9	Is phasing or timing of events decisions important?	Not clear	In smokers, if lung cancer occurs before bronchitis, then patient may die before bronchitis occurs	Possible to have different branches in the decision tree but Markov model or simulation may be necessary. (rows 2 to 4)

I10	Is there interaction directly between patients?	No	Infectious disease models	Models with interaction (rows 3, 4)
I11	Is there interaction due to constrained resources?	No	Models with resource constraints	Models with interaction (rows 3, 4)
I12	Could many events occur in one time unit?	No	Disaster, outbreak of infection, risk of co-morbidities (e.g. diabetes)	Need for small time intervals or continuous time models (row 4)
I13	Are interactions occurring in small populations?	No	Use in hospital catchments area rather than nationally	Need to consider individual level modelling because of the inaccuracies in using fractions of individuals (columns C, D, rows 3, 4)
I14	Are there delays in response due to resource constraints which then affect cost or health outcome	No	Rapid treatment with angioplasty and stents after a myocardial infarction	Need for stochastic output and interaction (columns C, D, rows 3, 4)
I15	Is there non-linearity in system performance when inherent variability occurs?	No	A marginal change in parameters produces a non-linear change in the system ITU is suddenly full and newly arriving patients must transfer elsewhere	DES useful

Adapted from: Brennan A, Chick S, Davies R. A Taxonomy of Model Structures for Economic Evaluation of Health Technologies. Health Econ. 2012; 15: 1295–1310 (95)

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Mortality

Assumption 1: Mortality of patients is fully determined by their type of lipodystrophy and level of organ abnormality.

Justification: We estimate a Cox proportional hazards model of patient survival using the number of organs impaired and the type of lipodystrophy (GL or PL) as covariates. The model yields a statistically significant (at 1%) coefficient on number of organs impaired, which remains significant in the presence of additional control variables such as patient demographics and lab values (see Table 75 in Appendix 17.6 for details). We interpret this result as implying that the number of impaired organs has a significant (negative) effect on mortality.

Assumption 2: Mortality depends on a patient's total number of organs impaired in a proportional manner.

Justification: This assumption is a premise of the Cox proportional hazards model. We test it using a Schoenfeld residual test, and find that the null hypothesis of a constant proportional relationship between the hazard rate of dying and the number of organs impaired is not rejected (see Table 74 in Appendix 17.6).

Assumption 3: Overall mortality of PL patients treated with metreleptin does not differ from the general population (adjusted for age and gender); however, amongst PL patients those with great organ abnormalities experience greater mortality (per assumption 2).

Justification: PL patients from the GL/PL natural history study were not observed to experience mortality in excess of the general public (conditional on age and gender). Among PL patients in the NIH follow-up study, only one mortality was observed.

Treatment efficacy

Assumption 4: Patients retain the same level of attribute impairment (other than organ abnormality) throughout the course of the model.

Justification: As lipodystrophy is a chronic condition, patients not treated with metreleptin remain with the same level of impairment. It is also likely that standard of care patients get worse on other attributes and do so faster than treated patients, but the model does not account for this outside of organ abnormality. This is borne out by evidence from the GL/PL natural history study.

Assumption 5: Laboratory attribute levels (Triglycerides and HbA1c levels) of metreleptin treated patients follow the observed patient data from the NIH when available and otherwise remain unchanged. Organ abnormalities progress as per assumption 2. Other attributes reflect observed patient data at baseline and a composite indicator for improvement for period 1 and subsequent periods.

Justification: We use real world data on the evolution of treated patients' attributes, when possible. However, precise dates regarding improvement in attributes other than laboratory values and organ abnormalities were not consistently collected and thus these data are only used to indicate the status of the attribute before (baseline) and after metreleptin initiation.

Medical costs

Assumption 6: Medical treatment costs are derived for each lipodystrophy-related organ abnormality and level of triglyceride/glucose HbA1C non-response based on key opinion leader estimates of resource utilization and corresponding NHS reference costs.

Justification: Medical treatment costs are not available in the existing literature, therefore key opinion leaders from the UK were consulted to provide an estimate of real world resource use.

Assumption 7: Medical treatment costs for each lipodystrophy-related organ abnormality are assigned to each period of the model by multiplying a patient's probability of having the specified type of organ abnormality with their probability of survival and the medical cost of treating the complication (discounted to present value).

Justification: This approach is a standard way of calculating expected costs (or other values of interest) whenever there is uncertainty over the outcomes that may arise, and probabilities quantifying this uncertainty.

Assumption 8: Standard of care treatment costs are considered for both standard of care and metreleptin treatment arms

Justification: Patients in both the standard of care and metreleptin treatment arms were assumed to receive standard care of therapy throughout the 60-year model time frame. The assumption that SoC does not change over this time horizon with the introduction of metreleptin is a potentially conservative one as metreleptin may also be expected to displace insulin use as part of SoC.

Utilities

Assumption 9: Utility decrements are derived for each attribute level based on results from a discrete choice experiment (DCE). The decrements are used in unmodified form even though characteristics valued by the DCE were similar but not identical to characteristics collected in the NIH Study and used to populate the model.

Justification: The characteristics in the DCE were similar to those collected in the NIH study and the effect of changes in decrement values was explored in model sensitivity analysis.

Organ abnormality progression

Assumption 10: Organ abnormality progression follows a Markov process once metreleptin patients are no longer observed in the underlying real-world data and from baseline for patients not on metreleptin.

Justification: Please refer to the survival study in Appendix 17.6

Assumption 11: Organ abnormality progression is due to the underlying disease and thus patients who are observed to develop new abnormalities while on metreleptin during the NIH follow up study would have develop the new abnormalities in the absence of metreleptin treatment as well.

Justification: Please refer to the survival study in Appendix 17.6

12.1.6 Define what the model’s health states are intended to capture.

In the modelling approach adopted (see Section 12.1.4), an individual patient's health is characterized by different attributes related to key efficacy outcomes such as liver abnormality, heart abnormality, kidney abnormality, pancreas abnormality, retinopathy, neuropathy, amputation, impaired physical appearance, hyperphagia and female reproductive dysfunction/infertility. At each point in time, the values of these attributes collectively define each individual patient's health state.

Please refer to section 10.1.1 for a detailed description of the disease attributes.

Table D36: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	60 years	NICE recommends a time horizon to reflect the differences between costs and outcomes between alternative technologies. In order to reflect the life-long nature of lipodystrophy, the base case model time horizon is 60 years.	Section 12.1.4
Discount of 3.5% for costs	3.5%	NICE reference case criteria	Section 12.3.1
Perspective (NHS/PSS)	UK NHS PSS perspective	NICE reference case criteria	Section 12.3.1
Cycle length	1 year		Section 12.1.4
Baseline characteristics	Populated for each treatment arm from baseline data for 112 patients from NIH study, 80 of whom are included in label indication (base case)	Ensures consistency with observed patient data and with expected EMA label.	Section 12.1.4
Discontinuations	2.05%	Metreleptin discontinuation based on observed discontinuation in patient data. Once patient data are not available, the default annual discontinuation rate of 2.05% is applied.	
NHS, National Health Service; PSS, Personal Social Services			

12.2 Clinical parameters and variables

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

The clinical evidence data used in the cost-effectiveness analysis were generated from the observed patient data from the NIH study and the GL/PL natural history study. The NIH data measured at the time or enrolment was used for baseline attribute levels for patients in both treatment and SOC arms. The evolution of impairment to the attributes of patients in the treatment arm uses the observed data in the NIH study until the end of data availability (15 years). For patients in the standard of care treatment arm and metreleptin patients beyond the period of data availability, survival curves were generated from the NIH study. These survival curves were then scaled using the Cox model's coefficient generated from the GL/PL natural history study to estimate the effect of organ abnormality on mortality. The GL/PL natural history study was also used to derive organ abnormality progression probabilities. The details of how the clinical evidence is used to inform efficacy and mortality inputs are explained below:

Efficacy inputs:

- Treatment response with metreleptin from the NIH Follow-Up Study: all patients in the NIH Follow-Up Study were treated with metreleptin in a single arm clinical trial. Treatment response to metreleptin is observed for each patient until the end of data availability; beyond which, all patient attributes other than organ abnormality are assumed to remain constant at each patient's last observed value.

- Organ abnormality progression probabilities from the GL/PL natural history study: organ progression is modelled using probabilities estimated from the NIH study (for treated patients) and matched patients from the GL/PL natural history study (for standard of care patients). See the survival appendix for details.

Mortality inputs:

- Survival information for patients treated with metreleptin from the NIH Follow-Up Study to end of data availability.

- Time-varying Cox proportional hazards model is used to estimate the relationship between organ abnormality and mortality. This relationship is then applied to the NIH Follow-Up survival data to generate survival curves for each level of organ abnormality (see the survival appendix for more details).

- Mortality data from the National life tables in England released in September 2017 from the Office for National Statistics are used for patients with PL from the end of the NIH Follow-Up study until the end of the model time horizon

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Clinical outcomes are extrapolated beyond the study follow-up period; Impairment to attributes (other than organ abnormality) is assumed to remain at the final level achieved at the end of the follow-up period (15 years). The number of organs with abnormalities, on the other hand, is assumed to increase beyond that at the end of follow-up according to the specified transition probabilities. These probabilities characterise the likelihood of developing abnormality to an additional organ and are derived from patient data in the GL/PL natural history study and the NIH follow-up study.

Survival curves are also extrapolated beyond the study period. To do so, we fit parametric curves onto the empirical survival probability data in the 15-year study period, then use the estimated parameters to predict survival probabilities beyond the end of follow-up. We use extrapolation approaches described in Latimer (2013) (96) and Williams (2017).(97) We fit Exponential, Weibull, Log-Normal and Log-Logistic curves to the empirical survival data from the trial. We ran statistical goodness-of-fit

tests to select the curve that best approximates our data (see 17.6.2.2 for results and estimated curves), concluding that the exponential curve fits our data best for GL patients. In the base model, the observed survival probabilities are used for the first 16 periods (reflecting the maximum follow-up in the NIH study) and survival probabilities from the exponential curve is used thereafter. There were few deaths among patients with PL in the trial's small sample, that the estimated survival curve implied a mortality rate that is lower than the general population's. As such, we use age and gender appropriate survival from the National life tables in England to extrapolate beyond the real-world data and include organ abnormality-specific extrapolated curves following each parameterization for the full NIH population (GL and PL) shifted by the hazard ratio associated with PL as sensitivities.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

We assume that organ abnormality (an intermediate outcome) determines a patient's survival probabilities. This assumption is confirmed by the results of a Cox proportional hazards model estimated on data from the GL/PL natural history study (see assumption 1 and 2, and justifications as well as appendix 17.6, for more details).

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Hypoglycaemia was included in the cost-effectiveness analysis as an adverse event. Only treated patients were eligible to experience hypoglycemia and during the NIH study data period, a count of observed hyperglycemia events was assigned to each patient. After the end of observation, an annualized count of hyperglycemia events was assigned to remaining model periods.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Please refer to section 10.1.10.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table x below.

Table D37 displays the key inputs used to populate the economic model. The table also links to the description of the data in the appropriate sections of the submission document.

Table D37: Summary of variables used in the cost-effectiveness analysis

Parameters	Base case input	Reference
Utility		
Heart Abnormality	[redacted]	Section 10.1.9
Liver Abnormality	[redacted]	Section 10.1.9
Pancreas Abnormality	[redacted]	Section 10.1.9
Kidney Abnormality	[redacted]	Section 10.1.9
Hyperphagia	[redacted]	Section 10.1.9
Disruption to female reproductive function	[redacted]	Section 10.1.9
Loss of ability to perform work / school	[redacted]	Section 10.1.9
Impaired Physical Appearance	[redacted]	Section 10.1.9
Triglycerides: Achieved Goal (<=200 mg/dL)	[redacted]	Section 10.1.9
Triglycerides: Partial Response (>200 mg/dL, <=500 mg/dL)	[redacted]	Section 10.1.9
Triglycerides: No Response (>500 mg/dL)	[redacted]	Section 10.1.9
HbA1C: Hypoglycemia	[redacted]	Section 10.1.9
HbA1C: Achieved Goal (>4.0, <=7.0)	[redacted]	Section 10.1.9
HbA1C: Partial Response (>7.0%, <=8.0%)	[redacted]	Section 10.1.9
HbA1C: No Response > 8.0%	[redacted]	Section 10.1.9
Annual cost of lipodystrophy-related complications		
Heart Abnormality	£1,094	Section 12.3.7
Liver Abnormality	£528	Section 12.3.7
Pancreas Abnormality	£44	Section 12.3.7
Kidney Abnormality	£590	Section 12.3.7
Hyperphagia	£0	Section 12.3.7
PCOS (Females Only)	£0	Section 12.3.7
Unable to Perform School Work	£0	Section 12.3.7
Impaired Physical Appearance	£0	Section 12.3.7
Triglycerides: Achieved Goal (<=200 mg/dL)	£0	Section 12.3.7
Triglycerides: Partial Response (>200 mg/dL, <=500 mg/dL)	£0	Section 12.3.7
Triglycerides: No Response (>500 mg/dL)	£0	Section 12.3.7
HbA1C: Achieved Goal (>4.0, <=7.0)	£0	Section 12.3.7
HbA1C: Partial Response (>7.0%, <=8.0%)	£0	Section 12.3.7
HbA1C: No Response > 8.0%	£0	Section 12.3.7

Annual treatment costs per patient		
Metreleptin (£)	£852,858.75 per year for 10mg dose £434,633 per year when all vial sizes are available	Section 12.3.4
Standard of care (£)	£3,000	Section 12.3.4
Model Specifications		
Discount rate (costs)	3.5%	Section 12.1.7
Discount rate (life years and QALYs)	3.5%	Section 12.1.7
Model horizon (years)	60	
Per period (year) organ abnormality transition probabilities for metreleptin patients		
0 organs damaged to 1 organ damaged	5.4%	Section 17.6 - Survival Study
1 organs damaged to 2 organ damaged	5.0%	Section 17.6 - Survival Study
2 organs damaged to 3 organ damaged	8.3%	Section 17.6 - Survival Study
3 organs damaged to 4 organ damaged	3.9%	Section 17.6 - Survival Study
Per period (year) organ abnormality transition probabilities for nonmetreleptin patients		Section 17.6 - Survival Study
0 organs damaged to 1 organ damaged	9%	Section 17.6 - Survival Study
1 organs damaged to 2 organ damaged	17%	Section 17.6 - Survival Study
2 organs damaged to 3 organ damaged	12%	Section 17.6 - Survival Study
3 organs damaged to 4 organ damaged	6%	Section 17.6 - Survival Study
Assignment weight of organ damage of unknown organ to particular organs (see appendix 17.6.2.1 for details)		
Assignment weight: heart	45%	Section 12.1.3
Assignment weight: liver	94%	Section 12.1.3
Assignment weight: pancreas	39%	Section 12.1.3
Assignment weight: kidney	63%	Section 12.1.3

12.3 Resource identification, measurement and valuation

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

In terms of specialised service delivery, NHS England have already established a service specification (A03/S(HSS)/b) which includes the severe lipodystrophies which

may be treated with metreleptin. The specification covers the services provided at Cambridge University Hospitals (CUH) NHS Foundation Trust, both outpatient and, when indicated for initiation of therapy, inpatient. The covered population includes lipodystrophy patients as well as some potentially distinct sources of insulin resistance such as primary insulin receptoropathy. Services include diagnostic, therapeutic, and educational support to patients and care givers. Among the subset of patients in whom leptin therapy is initiated, the service specification already makes accommodation for additional visits to CUH specifically for treatment initiation and follow-up. Within the context of the overall service specification, only the cost of these additional visits could be considered specific to leptin treatment. Diagnostic, dietary, educational, and other costs associated with the service specification will be borne regardless, as would expense associated with therapies other than leptin. Hence, the introduction of metreleptin is not expected to involve any significant additional service infrastructure.

The NHS reference costs associated with lipodystrophy-related complications are detailed in Section 12.3.7. Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A systematic review of resource use and cost data was undertaken, using the same electronic medical databases and additional sources as presented in Section 11.1.3. Full details of the systematic review methods and the inclusion and exclusion criteria have been detailed in Appendix 17.4.

A total of 2,109 papers were identified from the electronic searches.

After removal of duplicates, 1,005 publications remained. After title and abstract screening, 997 publications were removed as these were not of relevance to the research question. These publications were excluded for reasons such as study type (n=395), date (n=206), outcome (n=131), duplicates (n=103), publication type (n=94) and population (n=68).

A total of 107 publications were assessed in full for further evaluation. Of these, 104 were excluded based on population (n=53), country (n=26), outcome (n=18), date (n=3), publication type (n=2) and study type (n=1). This left a total of three publications for data extraction; one paper considering HIV-associated lipoatrophy, one paper considering HIV-associated lipodystrophy and one paper considering HIV-associated lipodystrophy and lipoatrophy.

Three studies were identified contributing to the cost and resource use evidence: Piquet et al. (2007)(98), Llibre-Codina et al. (2007)(99) and Massella et al. (2011). Table D38 provides a summary of each of the papers identified in this review. All studies considered HIV-associated lipodystrophy or lipoatrophy and none of the studies provided relevant resource data for the NHS in England.

Table D38. Summary of papers identified in the cost and resource use review

Paper	Population	Perspective	Intervention	Cohort size	Source of data	Length of follow up	Cost year	Resources included
Piquet et al. (2007)(101)	Patients with HIV positive disease and facial lipoatrophy	NR	Polylactic acid Lipostructure	25	Prospective study across two hospitals in France	From January 2002 to December 2005	NR	Number of sessions
Llibre-Codina et al. (2007)(102)	Patients included in the trial were ≥18 years with confirmed HIV-1 infection, with ongoing HAART therapy and with a toxicity associated with an NRTI	Spanish societal perspective	HAART therapy	1,286 10.11% had lipodystrophy	Clinical trial Questionnaire completed by clinical experts Spanish specific cost sources	1 year	2005	Consultations, surgery, procedures, medicines, hospitalisations, job losses and other
Massella et al. (2011)(100)	Patients with HIV associated lipoatrophy, ≥18 years	Italian Service Suppliers' perspective	Immediate vs. delayed reconstructive treatment with poly-l-lactic acid or polyacrylamide gel	66 100% had lipoatrophy	Clinical trial	24 weeks	NR	Number of fillers, surgeon and assistant time
Key: HAART, highly active antiretroviral therapy; HIV, Human immunodeficiency virus; NR, not reported; NRTI, nucleoside analogue reverse transcriptase inhibitors								

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

Two clinical advisers who treat lipodystrophy at Addenbrooke's Hospital, part of CUH NHS Foundation Trust were asked to complete a resource use questionnaire to identify the type of frequency of services received by lipodystrophy patients. When the two advisors expressed differing impressions of resource use, the difference was discussed and resolved.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

The list price of metreleptin is £2,335 per vial 11.3mg (10mg dose). In light of per patient doses for UK patients enrolled in the early access programme, this corresponds to an annual per patient cost of £852,858.75

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

The primary analysis assumed an average per patient price of £434,633, based on the anticipated availability of smaller vial sizes, resulting in reduced wastage, within the next 3 months. The smaller vials are priced proportionally to the 11.3 mg vial (10mg dose) vial as follows: 5.8mg vial size (5mg dose) £1,167.50 and 3mg vial size (2.5mg dose) £583.80. The average price is computed from the distribution of observed current doses in the UK early access programme.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The costs associated with the technology and comparator are restricted to treatment costs. Drug administration costs such as home delivery and self-administration training are not separately included in this model as these activities will be funded by Aegerion Pharmaceuticals at no additional cost to patients or NHS. Additional resource use costs, such as laboratory tests and office visits, are difficult to quantify given the heterogeneity of disease characteristics and lack of quality data. In this model, the resource use costs are assume to occur equally to both metreleptin treated and standard of care patients and are thus reflected in the nominal "standard of care" costs that is assigned to all patients in the model.

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

In this model, each patient's health state is characterised by the presence or absence of a fixed set of attributes. The costs related to each attribute are reported in

Table D40. For each lipodystrophy-related complication, a per-period cost is calculated for each modelled patient based on their probability of having the complication and probability of survival in that period. Medical costs for each lipodystrophy-related complication or non-achievement of triglyceride and glucose HbA1C response are derived using resource utilisation estimates for each complication using a combination of KOL inputs and NHS reference costs. The detailed reference costs used for lipodystrophy-related complication are presented in Table D39.

Table D39: National Schedule of Reference costs associated with lipodystrophy-related complication

Lipodystrophy-related complications	HRG currency codes
Heart abnormality	Weighted cost of total HRGs currency codes relating to coronary artery bypass: ED22A, ED22B, ED22C, ED23A, ED23B, ED23C, ED24A, ED24B, ED24C, ED25A, ED25B, ED25C, ED26A, ED26B, ED26C, ED27A, ED27B, ED27C, ED28A, ED28B, ED28C - NHS Ref costs relating to coronary artery bypass
Renal abnormality	Total of pre-transplant costs, transplant costs, and follow up outpatient costs. Total of LA10Z £232.52, + weighted cost of pre-transplantation workup costs LA11Z LA12A LA12B £373.44, + weighted costs of examination post-transplantation £233.69, + weighted cost of kidney transplant = £15716.14, + outpatient attendances for service code 102 £307.09
Liver abnormality	Weighted cost of total HRGs currency code GA01A, GA01B, GA01C, + outpatient attendances for service code 102 £307.09
Pancreas abnormality	Weighted average cost per FCE of elective inpatients, non-elective long stays, non-elective short stays for endocrine disorders KA08A, KA08B, KA08C

The estimated cost per patient with organ abnormality is calculated with the following formula:

Estimated cost per patient with abnormality = (Number of lipodystrophy-related inpatient stays per annum per patient/ Fraction of patients with abnormality) * Cost per inpatient stay

Table D40: Estimated cost per patient with abnormality

Disease attribute	Estimated cost per patient with abnormality
Per-period medical costs from lipodystrophy-related complications	
Heart abnormality	£1,093.94
Renal abnormality	£590.04
Liver abnormality	£527.97
Pancreas abnormality	£44.28
Hyperphagia	£0
PCOS (Females Only)	£0
Unable to Perform School or Work	£0
Impaired Physical Appearance	£0
Per-period medical costs from non-achievement of triglyceride and/or glucose HbA1C response	
Triglycerides Control	
Triglycerides: Achieved Goal (<=200 mg/dL)	£0
Triglycerides: Partial Response (>200 mg/dL, <=500 mg/dL)	£0
Triglycerides: No Response (>500 mg/dL)	£0
Glucose Control	
HbA1C: Achieved Goal (<=7.0)	£0
HbA1C: Partial Response (>7.0%, <=8.0%)	£0
HbA1C: No Response > 8.0%	£0

In the primary cost-effectiveness analysis, no costs are associated with hyperphagia, PCOS, inability to perform school or work, impaired physical appearance, or abnormal laboratory levels. While these attributes may impose costs on either the patient or on the healthcare systems, the costs likely vary substantially and are hard to quantify. For example, PCOS can lead to fertility impairment and thus may imply large costs for adults who desire children. However, it may impose no cost for children.

As these attributes are more likely to be present in patients who do not receive metreleptin, including £0 in associated costs is conservative.

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all

adverse events and complication costs, both during and after longer-term use of the technology.

The cost of hypoglycaemic events is included in the model as an adverse event. The mean expenditure per hospital admission for hypoglycaemia was £1034. (103) The cost was inflated to the most recent prices using the PSSRU inflation indices 2016 HCHS index (http://www.pssru.ac.uk/pub/uc/uc2016/sources-of-information.pdf - section 16.3). Inflating £1034 to 2015/16 prices from 2012 prices using the PSSRU results in £1087.07 from calculation [1034 * (297.0/282.5)] where 297.0 refers to 2015/16 HCHS price index and 282.5 refers to 2011/12 price index.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Cost savings and additional costs have been described previously in this document. The model base case does not include costs to caregivers, costs associated with routine monitoring and drug administration costs such as home delivery and self-administration training

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Hyperphagia, PCOS (Females Only) and Unable to Perform School or Work are currently costed at £0 in the model. This provides additional opportunities for resource saving as hyperphagia, PCOS and unable to perform school or work represent substantial levels of unquantified health and non-health benefits in the QoL of carers/families of children and adults with lipodystrophy.

12.4 Approach to sensitivity analysis

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

We considered variations in structural assumptions based on the following scenarios: Results are reported in 12.5.16

- Future Price Changes: Loss of metreleptin exclusivity at 10 years
    - Assumes metreleptin list price falls 90% after loss of exclusivity
    - The model allows the user to select the year of the price change and the new price.
- Reduced initial price
- Elimination of mortality benefit of metreleptin for PL patients
    - Although organ abnormalities are associated with increased mortality in both GL and PL patients, the survival curve observed in the GL/PL natural history study does not substantially differ from that of the general population. Thus, we explore eliminating the mortality benefit of metreleptin for PL patients by predicting survival from the general population curve based on patient age, regardless of organ abnormality.
- Changes to assumptions regarding organ abnormality progression
    - Slower organ progression risk -- all organ progression probabilities for both metreleptin treated patients and standard of care patients can be increased or decreased in tandem
    - An alternative organ abnormality progression scenario for standard of care patients was assessed by assuming that standard of care patients develop organ abnormalities as observed in the GL/PL Natural History Study, without adjusting for differences in baseline characteristics between those patients and the patients in the NIH Follow-up study. (See Table 1 in appendix 17.6.1 for unadjusted natural history study progression probabilities.)
- Alternate survival extrapolation methods
    - The model allows for the user to toggle between various parameterizations used to extrapolate the GL survival curve observed in the NH trial
    - Additionally, the cox regression coefficient that determines how much mortality increases for each subsequent organ abnormality for GL patients can be varied by the user
- Earlier treatment initiation (Preliminary)
    - Preliminary adaptation of model focused on CGL patients only

- Considers scenario in which patients initiate treatment at age 1
- Further sensitivities of early treatment initiation to incorporate larger hyperphagia utility decrement and parental disutility

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Deterministic one-way sensitivity analysis has been conducted on the following variables, representing the key clinical and economic inputs into the economic model detailed in Table D41:

- Utility decrements
- Annual cost of lipodystrophy-related complications
- Annual treatment costs per patient
- Model specifications
  - Discount rate (costs)
  - Discount rate (life years and QALY)
  - Annual medical cost increase
  - Annual pharmacy cost increase
- Organ progression probabilities
- Relationship between organ abnormality and survival
- Time horizon (30 years)

Deterministic multi-way sensitivity analyses has also been conducted to reflect the following scenarios detailed in Table D42:

- Assumes a lower price for metreleptin
- Doubles the hyperphagia decrement
- Incorporates resolution of heart abnormalities for some patients who experience a resolution of hypertension

Base case parameters were chosen to capture the heterogeneity of the disease over time in a lipodystrophy patients. Probabilistic sensitivity analysis was undertaken based on the distribution assumptions and variables as detailed in Table D43. The model allows the user to consider a range of user selected variables for the PSA.

12.4.3 Complete Table D41,Table D42,Table D43 as appropriate to summarise the variables used in the sensitivity analysis.

Table D41: DSA one-way parameters

Variable	Description	Base case input	DSA Input	
			Low	High
Utility (Base case ± 50%)				
Heart abnormality	Heart abnormality utility decrement	-0.19	-0.09	-0.28
Liver abnormality	Liver abnormality utility decrement	-0.15	-0.08	-0.23
Pancreas abnormality	Pancreas abnormality utility decrement	-0.13	-0.06	-0.19
Kidney abnormality	Kidney abnormality utility decrement	-0.13	-0.06	-0.19
Hyperphagia	Hyperphagia utility decrement	-0.11	0.00	-0.22
Disruption to female reproductive function	Disruption to female reproductive function utility decrement	-0.06	-0.03	-0.09
Loss of ability to perform work / school work	Loss of ability to perform work / school work utility decrement	-0.25	-0.13	-0.38
Impaired physical appearance	Impaired physical appearance utility decrement	-0.10	-0.05	-0.15
Triglyceride control (<=200 mg/dL)	Triglyceride control utility decrement	0.00	0.00	0.00
Partial triglyceride response (>200 mg/dL, <=500 mg/dL)	Partial triglyceride response utility decrement	-0.05	-0.02	-0.07
No triglyceride response (>500 mg/dL)	No triglyceride response utility decrement	-0.11	-0.06	-0.17
Hypoglycemia	Hypoglycemia utility decrement	-0.01	-0.01	-0.02
HbA1C control (HbA1C > 4.0%, HbA1C <= 7.0%)	HbA1C control utility decrement	0.00	0.00	0.00
Partial HbA1C response (HbA1C > 7.0%, HbA1C <= 8.0%)	Partial HbA1C response utility decrement	-0.08	-0.04	-0.12
No HbA1C response (HbA1C > 8.0%)	No HbA1C response utility decrement	-0.18	-0.09	-0.27
Parental care	Parental care utility decrement	0	0.00	0.00
Fast Progression	Fast progression utility decrement	-0.16	-0.08	-0.24

Variable	Description	Base case input	DSA Input	
Annual cost of lipodystrophy-related complications (£0 to base case + 50%)				
Heart abnormality (£)	Heart abnormality annual cost	£1,094	£0	£1,641
Liver abnormality (£)	Liver abnormality annual cost	£528	£0	£792
Pancreas abnormality (£)	Pancreas abnormality annual cost	£44	£0	£66
Kidney abnormality (£)	Kidney abnormality annual cost	£590	£0	£885
Annual treatment costs per patient (base case ± 50%)				
Metreleptin (£)	Metreleptin annual cost	£852,858	£426,429	£1,279,288.13
Standard of care (£)	Standard of care annual cost	£3,000	£1,500	£4,500
Model specifications (base case ± 50%)				
Discount rate (costs; %)	Discount rate [costs]	3.5%	1.8%	5.3%
Discount rate (life years and QALYs; %)	Discount rate [life years and QALYs]	3.5%	1.8%	5.3%
Cox proportional hazard regression coefficient for number of organ abnormalities	Cox proportional hazard regression coefficient for number of organ abnormalities	1.09	0.275	1.904
Organ progression (base case ± 50%)				
0 organs damaged to 1 organ damaged [MET]	Organ abnormality progression [MET; 0 to 1 organs]	5%	0.0%	8%
1 organs damaged to 2 organ damaged [MET]	Organ abnormality progression [MET; 1 to 2 organs]	5%	0.0%	8%
2 organs damaged to 3 organ damaged [MET]	Organ abnormality progression [MET; 2 to 3 organs]	8%	0.0%	12%
3 organs damaged to 4 organ damaged [MET]	Organ abnormality progression [MET; 3 to 4 organs]	4%	0.0%	6%
0 organs damaged to 1 organ damaged [Non-MET]	Organ abnormality progression [Non-MET; 0 to 1 organs]	9%	0.0%	13%
1 organs damaged to 2 organ damaged [Non-MET]	Organ abnormality progression [Non-MET; 1 to 2 organs]	17%	0.0%	26%
2 organs damaged to 3 organ damaged [Non-MET]	Organ abnormality progression [Non-MET; 2 to 3 organs]	12%	0.0%	18%
3 organs damaged to 4 organ damaged [Non-MET]	Organ abnormality progression [Non-MET; 3 to 4 organs]	6%	0.0%	9%
Transition Probability Multiplier	Allows speed of organ abnormality progression to be scaled for both MET and non-MET patients	100%	50%	150%
Time Horizon				

Variable	Description	Base case input	DSA Input	
Time horizon: 60 years (base case)				
Time horizon: 30 years				

The deterministic multi-way scenario implements the following changes to the base case for the label indication group:

Table D42: DSA multi-way parameters

Variable	Description of DSA change	Base case input	Scenario input
List Price	Assumes a lower price for metreleptin ([redacted]	£[redacted]/ per patient (per year)	£[redacted]patient (per year)
Hyperphagia utility decrement	Doubles the hyperphagia decrement	-0.11	-0.22
Period 1 heart abnormalities for metreleptin patients	Incorporates resolution of heart abnormalities for some patients who experience a resolution of hypertension	As reported in NIH study, assuming baseline abnormalities continue	As reported in NIH study, assuming baseline abnormalities resolve for patients who are prehypertensive at baseline but have normal blood pressure in period 1

Table D43: PSA parameters

Variable	Mean	Standard Deviation	Distribution
Standard of care (£)	3000	750	Gamma
Metreleptin (£)	217316.726	54329.18149	Gamma
Heart abnormality	-0.186531291	-0.046632823	Beta
Liver abnormality	-0.153133609	-0.038283402	Beta

Variable	Mean	Standard Deviation	Distribution
Kidney abnormality	-0.128145147	-0.032036287	Beta
Hyperphagia	-0.113407277	-0.028351819	Beta
Disruption to female reproductive function	-0.058149567	-0.014537392	Beta
Loss of ability to perform work / school work	-0.254734725	-0.063683681	Beta
Impaired physical appearance	-0.100666155	-0.025166539	Beta
Pancreatitis	-0.128	-0.032	Beta
Hypoglycemic Events	-0.014964286	-0.003741072	Beta
Fast progression	-0.16	-0.04	Beta
No Response (HbA1C)	-0.18	0.045	Beta
Partial Response (HbA1C)	-0.08	-0.02	Beta
No Response (Triglycerides)	-0.112337353	-0.028084338	Beta
Partial Response (Triglycerides)	-0.047523742	-0.011880936	Beta
0 organs damaged to 1 organ damaged [MET]	0.055	0.01375	Normal
1 organs damaged to 2 organ damaged [MET]	0.051	0.01275	Normal
2 organs damaged to 3 organ damaged [MET]	0.0869	0.021725	Normal

Variable	Mean	Standard Deviation	Distribution
3 organs damaged to 4 organ damaged [MET]	0.0399	0.009975	Normal
0 organs damaged to 1 organ damaged [Non-MET]	0.0888	0.019175	Normal
1 organs damaged to 2 organ damaged [Non-MET]	0.1725	0.041375	Normal
2 organs damaged to 3 organ damaged [Non-MET]	0.1229	0.037925	Normal
3 organs damaged to 4 organ damaged [Non-MET]	0.0622	0.0140425	Normal
Discontinuation Rate	0.017423327	0.004355832	Normal
Cox proportional hazard regression coefficient for number of organ abnormalities	1.0897	0.4155	Normal
Universal Progression Multiplier	1	0.25	Normal
Discount Cost	0.035	0.00875	Normal
Discount QALY/LY	0.035	0.00875	Normal

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

All parameters above were used in the sensitivity analysis.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

The following presents the base case incremental results comparing metreleptin to SoC over a 60-year time horizon, assuming availability of vials for the 2.5mg, 5mg, and 10mg doses of metreleptin at list price. The results of the base-case ICER with the patient access scheme are presented in a separate document (refer to the HST PAS Evidence Submission).

Table D44: Cost-effectiveness results for label indication group for 10mg dose (Base case 1)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (60 years)			
Cost of Therapy(£)	£10,909,179	£41,026	£10,868,153
Other Medical Costs(£)	£24,969	£23,125	£1,844
Total Costs (£)	£10,934,148	£64,151	£10,869,997
Treatment effectiveness per patient (60 years)			
Life Years (Years)	17.95	13.68	4.27
Utility Decrements (QALYs)	-9.48	-13.32	3.84
Quality-Adjusted Life Years (QALYs)	8.47	0.36	8.11
Cost-effectiveness (60 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			£1,340,457

Table D45: Cost-effectiveness results for label indication group for multiple vials (Base case 2)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (60 years)			
Cost of Therapy(£)	£5,585,927	£41,026	£5,544,900
Other Medical Costs(£)	£24,969	£23,125	£1,844
Total Costs (£)	£5,610,896	£64,151	£5,546,744
Treatment effectiveness per patient (60 years)			
Life Years (Years)	17.95	13.68	4.27
Utility Decrements (QALYs)	-9.48	-13.32	3.84
Quality-Adjusted Life Years (QALYs)	8.47	0.36	8.11
Cost-effectiveness (60 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			£684,009

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The outcomes from the model were not compared with the clinical trial results as no randomised controlled trial of metreleptin in lipodystrophy patients has been conducted, largely due to the extreme rarity and severity of the condition.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

This does not apply to the individual patient model.

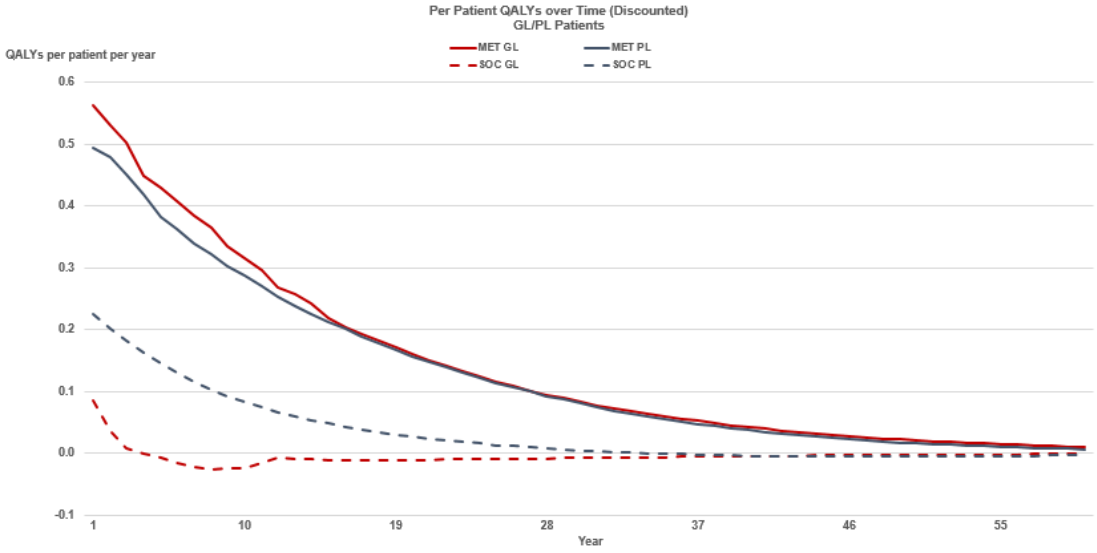
12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs accrue to patients on a per-period basis over the course of 60 one year periods. A patient's attribute profile in each period generates a QALY decrement that is subtracted from 1–the utility from perfect health. QALYs are then summed across all periods in the model, with each period's QALY value discounted appropriately. QALYs are also scaled by the survival probabilities of patients. Since attribute impairment is stochastic, QALY decrements arise with some likelihood in each period and are scaled by the appropriate probability.

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

In the model, LY and QALYs accrue over a period of 60 years. The per patient QALYs over time are presented in Figure D26.

Figure D26: Per Patient QALYs over Time (Discounted) (BC1 and BC2)



12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

The figures below display each associated health condition's incremental impact on period 1 QALYs for metreleptin and SOC patients. Overall, an average metreleptin

patient will experience a year of life equivalent to nearly half of one lived in perfect-health while the average standard of care patient will experience a year of life equivalent to nearly one-third of one lived in perfect-health and about three-fifths of one lived while treated with metreleptin. While the assumption that a lipodystrophy patient with none of the specified attributes would experience perfect health is unrealistic, subtracting the utility decrements from a lower base results in a number of standard of care patients receiving negative utility. The difference in per period utility between metreleptin treated and standard of care patients does not depend on the value assigned to perfect health, the choice to not adjust the QALY base seems reasonable.

Figure D27: Utility decrements in period 1 (MET patients) (BC1 and BC2)

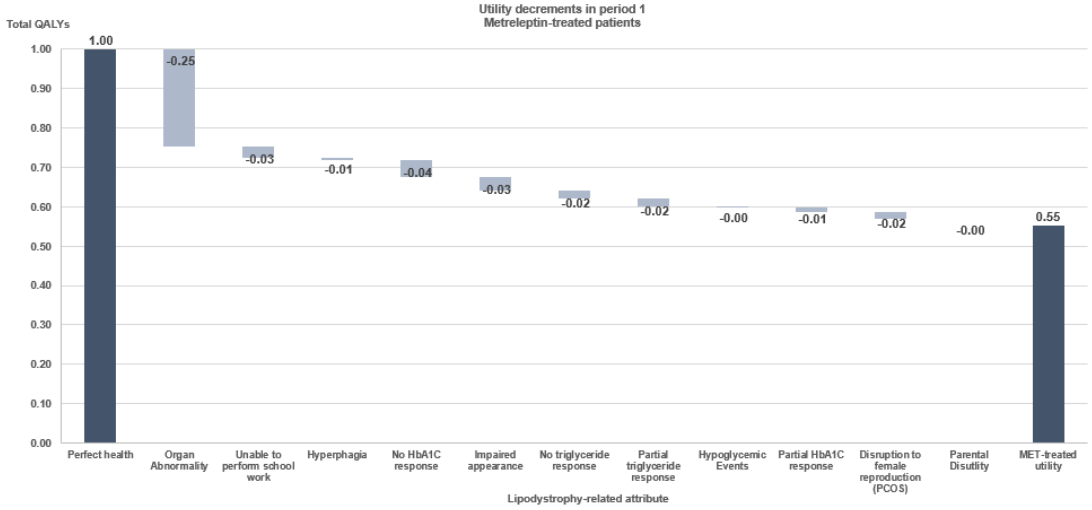
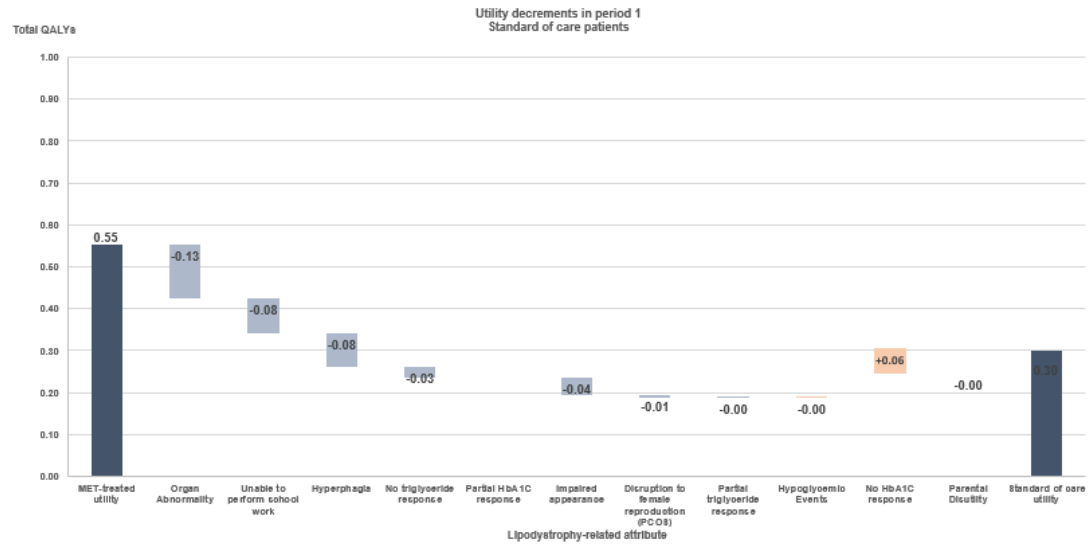


Figure D28: Utility decrements in period 1 (SOC patients) (BC1 and BC2)



12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table D46: Undiscounted incremental QALYs for label indication group (BC1 and BC2)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Treatment effectiveness per patient (60 years)			
Life Years (Years)	35.71	24.71	11.00
Utility Decrements (QALYs)	-20.42	-24.06	3.64
Quality-Adjusted Life Years (QALYs)	15.30	0.65	14.64

12.5.8 Please provide undiscounted incremental costs for the intervention compared with each comparator

Table D47: Undiscounted costs for label indication group for 10mg dose (BC1)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Treatment effectiveness per patient (60 years)			
Cost of Therapy	£19,273,545	£74,129	£19,199,416
Other Medical Costs	£54,874	£43,822	£11,052
Total Costs	£19,328,419	£117,951	£19,210,468

Table D48: Undiscounted costs for label indication group for multiple vials (BC2)

Metreleptin vs.SOC	Metreleptin	SOC	Increment
Treatment effectiveness per patient (60 years)			
Cost of Therapy	£9,874,711	£74,129	£9,800,582
Other Medical Costs	£54,874	£43,822	£11,052
Total Costs	£9,929,585	£117,951	£9,811,634

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Not applicable.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not applicable.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in Table D41.

The results of the deterministic sensitivity analysis are presented in Figure D29 and Figure D30.

Figure D29: DSA one-way results for 10mg dose (based around BC1)

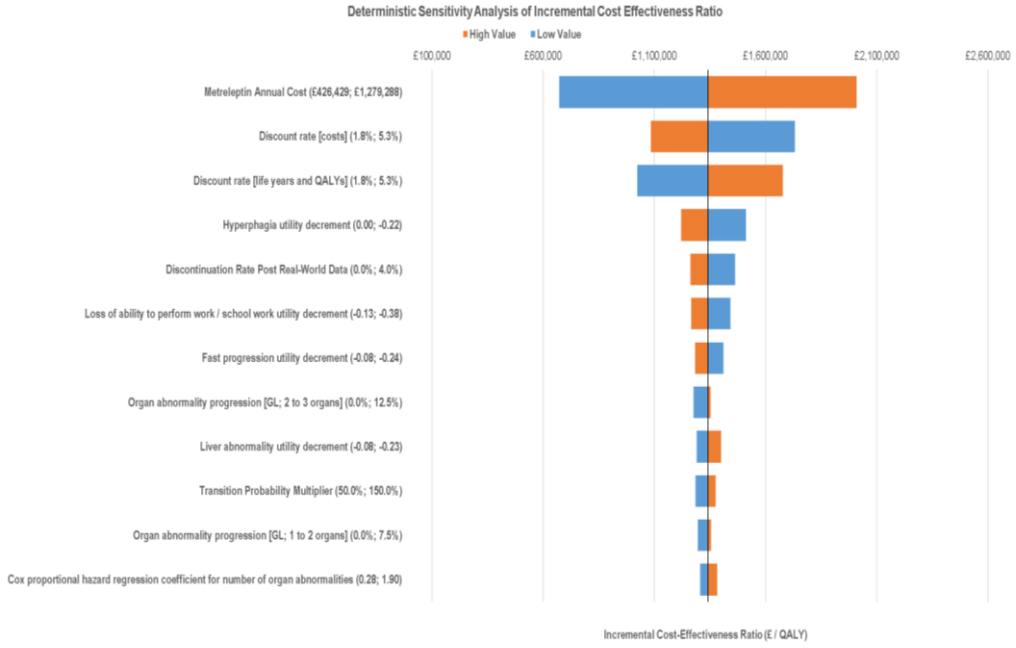
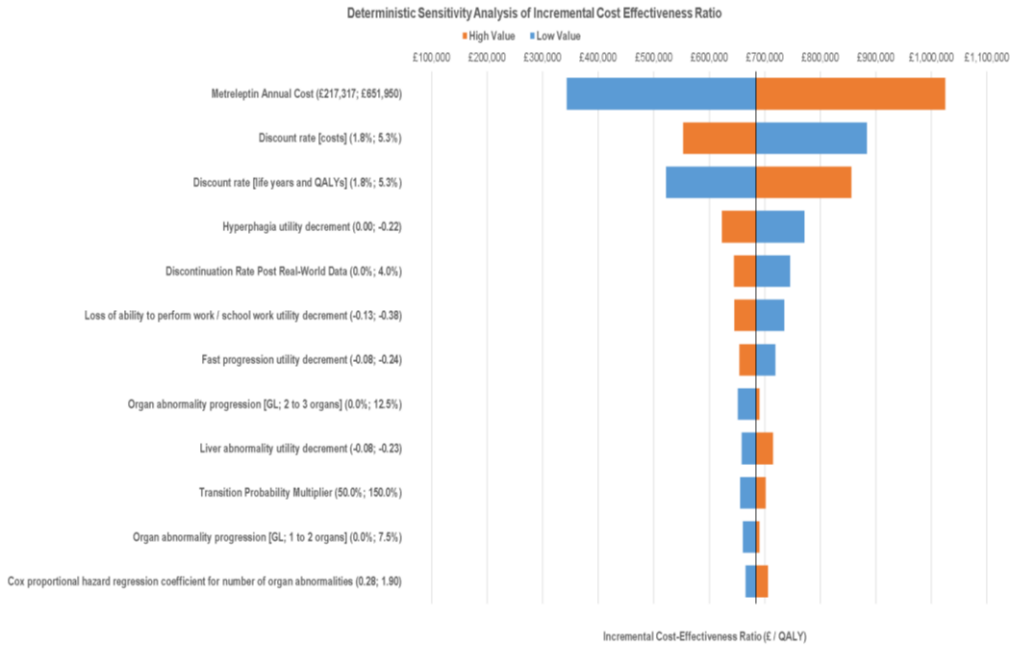


Figure D30: DSA one-way results for multiple vials (based around BC2)



12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table Table D42.

The deterministic multi-way scenario implements the following changes to the base case for the label indication group:

- Reduces the list price by [redacted]
- Doubles the hyperphagia decrement to -0.22
- Incorporates resolution of heart abnormalities for some patients who experience a resolution of hypertension

Table D49: DSA multi-way scenario results for 10mg doses (based around BC1)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (60 years)			
Cost of Therapy(£)	£11,039,566	£41,113	£10,998,453
Other Medical Costs(£)	£23,631	£23,135	£496
Total Costs (£)	£11,063,197	£64,249	£10,998,949
Treatment effectiveness per patient (60 years)			
Life Years (Years)	18.17	13.70	4.46
Utility Decrements (QALYs)	-9.40	-14.30	4.90
Quality-Adjusted Life Years (QALYs)	8.77	-0.60	9.37
Cost-effectiveness (60 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			£1,174,305

Table D50: DSA multi-way scenario results for multiple vials (based around BC2)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (60 years)			
Cost of Therapy(£)	£5,652,706	£41,113	£5,611,593
Other Medical Costs(£)	£23,631	£23,135	£496
Total Costs (£)	£5,676,337	£64,249	£5,612,088
Treatment effectiveness per patient (60 years)			
Life Years (Years)	18.17	13.70	4.46
Utility Decrements (QALYs)	-9.40	-14.30	4.90
Quality-Adjusted Life Years (QALYs)	8.77	-0.60	9.37
Cost-effectiveness (60 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			£599,175

12.5.13 Present results of the probabilistic sensitivity analysis described in Table D43.

Figure 31: Scatterplot PSA results for multiple vials (BC2)

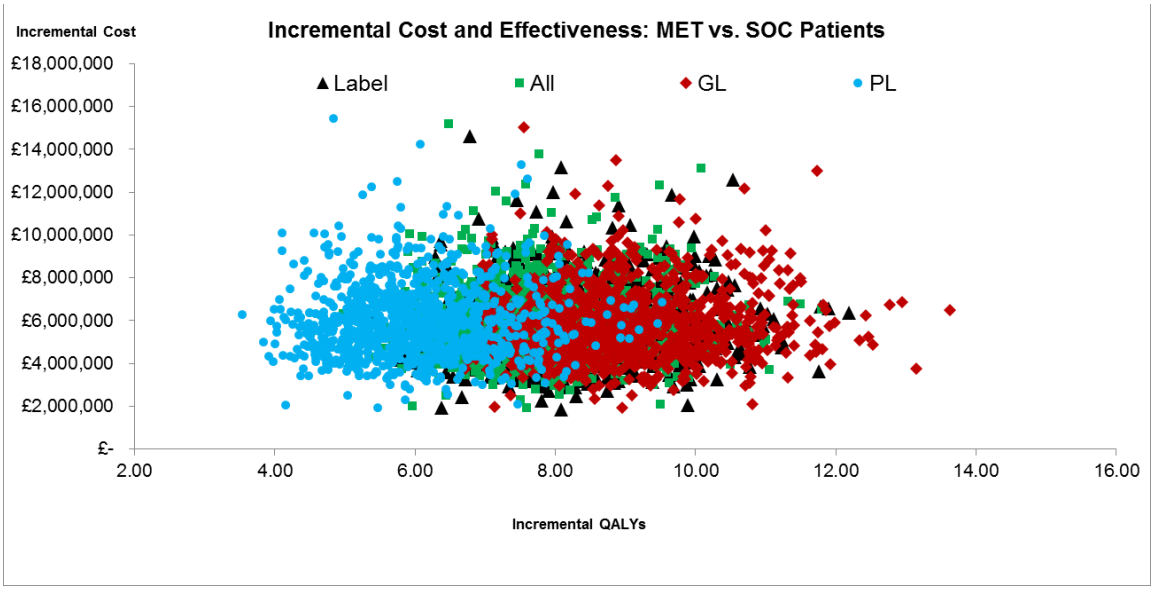
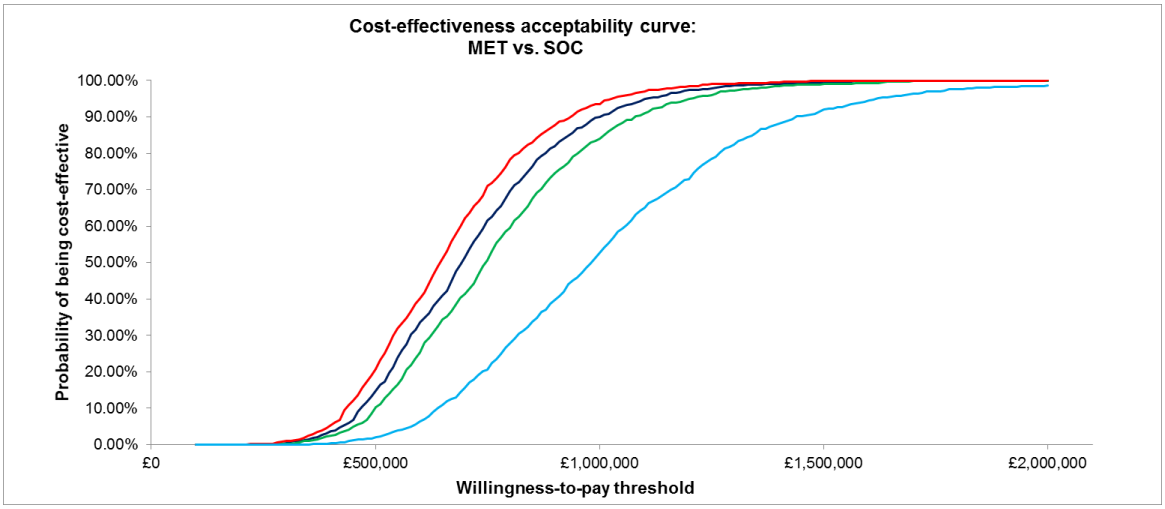


Figure 32: Cost-effectiveness acceptability curve for multiple vials (BC2)



12.5.14 What were the main findings of each of the sensitivity analyses?

The ICER and QALYs vary as expected as price and utility decrements are varied. While the range of QALYs is significant metreleptin is associated with significant QALY gain in all scenarios as seen in

Table D52.

Table D51: Scenario analysis results for 10mg dose (BC1)

Structural Scenario	Specific Assumptions/Inputs	ICER	QALYs Gained
Base case	List price, with multiple vial sizes	£1,340,457	8.11
Base case plus assume [redacted] lower price for metreleptin	List price with 50% discount, with multiple vial sizes	£[redacted]	8.11
Base case plus alternate inputs	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	£1,174,305	9.37
Base case plus alternative inputs assume [redacted]	List price with 50% discount, with multiple vial sizes, doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	[redacted]	9.37
Future Price Changes: Loss of metreleptin exclusivity	Metreleptin list price falls 90% after 10 years	£746,788	8.11
Elimination of mortality benefit of metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ abnormality.	£1,343,703	8.10
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	£1,374,718	7.74
	all organ progression probabilities decreased by 50%	£1,284,550	8.64
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	£1,337,257	8.13
Alternate survival extrapolation methods: GL curve parameterization	Weibull	£1,355,200	7.81
	Log Normal	£1,333,413	8.24
	Logit	£1,341,641	8.08
Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	£1,304,693	8.11
	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	£1,382,635	7.92

Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	£1,291,187	8.05

Table D52: Scenario analysis results for multiple vials (BC2)

Structural Scenario	Specific Assumptions/Inputs	ICER	QALYs Gained
Base case	List price, with multiple vial sizes	£684,009	8.11
Base case plus assume [redacted] lower price for metreleptin	List price with [redacted], with multiple vial sizes	[redacted]	8.11
Base case plus alternate inputs	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	£599,176	9.37
Base case plus alternative inputs and [redacted] price for metreleptin	List price with [redacted] with multiple vial sizes, doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	[redacted]	9.37
Future Price Changes: Loss of metreleptin exclusivity	Metreleptin list price falls 90% after 10 years	£380,632	8.11
Elimination of mortality benefit of metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ abnormalitye.	£685,643	8.10
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	£701,475	7.74
	all organ progression probabilities decreased [redacted]	[redacted]	8.64
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	£682,354	8.13
Alternate survival extrapolation methods: GL curve parameterization	Weibull	£691,495	7.81
	Log Normal	£680,435	8.24
	Logit	£684,222	8.08
	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	£665,472	8.11

Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	£705,809	7.92
Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	£659,036	8.05

12.5.15 What are the key drivers of the cost results?

The key cost drivers in the individual patient model are the annual price of Metreleptin, the discount rate applied to treatment costs as well as patient life years and QALYs, and the utility decrement associated with hyperphagia. As depicted in the above deterministic sensitive analysis, however, many variables, especially those related to utility decrements and probabilities of increased organ abnormality, have an incremental impact on the ICER estimate.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

The results of the preliminary analysis of early initiation, describe in 12.4.1, are not described elsewhere and are shown in

Table D53 below.

Table D53: Early treatment initiation at age 1 results (CGL)

Structural Scenario	Specific Change	ICER	QALYs Gained
Early treatment initiation at age 1: CGL	List price, multiple vial sizes (No Discount)	846,380	12.06
	List price, multiple vial sizes plus double hyperphagia decrement, plus parental disutility of -0.05 per period	726,962	14.04

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

Subgroups included in the model were identified based on the labelled indication. The following subgroups were included:

- Generalised lipodystrophy meeting labelled indication (GL) (n=63)
- Partial lipodystrophy patients meeting labelled indication (PL) (n=17)
- All NIH patients (n=112), including those who do not meet the labelled indication
- Congenital generalised lipodystrophy, including those who do not meet the labelled indication (CGL) (n=48)

12.6.2 Define the characteristics of patients in the subgroup(s).

Lipodystrophy may be either congenital (inherited) or acquired and may be generalised (affecting adipose tissue throughout the body) or partial, affecting adipose tissue in parts of the body. While heterogeneous in aetiology and manifestation, metabolic abnormalities, progressive abnormality to organs, hypoleptinaemia (low leptin), and favourable response to metreleptin are commonly observed across patients.

The severity and burden of lipodystrophy is consistently high among patients with generalised lipodystrophy (GL). The GL subgroup is consistent with the labelled

indication, patients with congenital or acquired GL, in adults and children 6 years of age and above.

The presentation of partial lipodystrophy (PL) is more heterogeneous, with some patients exhibiting more severe metabolic complications. The indication being sought within PL includes the group of patients with more severe metabolic abnormalities regardless of standard treatment and lower leptin levels. The PL subgroup is consistent with the labelled indication, patients with familial or acquired PL, characterised by leptin level < 12 ng/ml with triglycerides > 500 mmol/l and/or HbA1c > 8 %, in adults and children 12 years of age and above uncontrolled on standard therapy.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

The subgroup analysis is conducted by restricting the results from the model to those associated with only patients who meet the subgroup criteria. For instance, in the GL subgroup analysis, only patients who met the label indication and who had GL were included, so the model results were averaged across these 63 patients rather than all 80 patients who met the label indication.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Table D54: Discounted subgroup results for 10mg dose (BC1)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	18.91	15.49	8.35	0.56	-0.41	-0.79	£1,440,200
GL	63	17.25	12.02	8.50	-0.55	-0.38	-0.83	£1,199,812
PL	17	20.49	19.82	8.35	3.73	-0.43	-0.66	£2,359,642
CGL	48	18.40	13.12	9.22	-0.65	-0.39	-0.86	£1,244,737

Table D55: Undiscounted subgroup results for 10mg dose (BC1)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	38.47	29.66	15.23	1.41	-0.43	-0.80	£1,459,627
GL	63	34.61	21.07	15.52	-0.92	-0.39	-0.84	£1,171,292
PL	17	39.80	38.19	14.46	6.48	-0.44	-0.68	£2,386,596
CGL	48	37.16	23.35	16.98	-1.15	-0.40	-0.87	£1,178,701

Table D56: Discounted subgroup results for all vial sizes (BC2)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	18.91	15.49	8.35	0.56	-0.41	-0.79	£734,643
Generalised lipodystrophy (GL)	63	17.26	12.02	8.50	-0.55	-0.38	-0.83	£612,443
Partial lipodystrophy (PL)	17	20.49	19.82	8.35	3.73	-0.43	-0.66	£1,202,614
Congenital generalised lipodystrophy (CGL)	48	18.40	13.12	9.22	-0.65	-0.39	-0.86	£621,110

Table D57: Undiscounted subgroup results for all vial sizes (BC2)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	38.47	29.66	15.23	1.41	-0.43	-0.80	£745,057
Generalised lipodystrophy (GL)	63	34.61	21.07	15.52	-0.92	-0.39	-0.84	£598,546
Partial lipodystrophy (PL)	17	39.80	38.19	14.46	6.48	-0.44	-0.68	£1,216,530
Congenital generalised lipodystrophy (CGL)	48	37.16	23.35	16.98	-1.15	-0.40	-0.87	£602,159

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

All subgroups identified are included in the submission.

12.7 Validation

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The approach to the model has been validated with leading lipodystrophy clinical experts including Dr. Rebecca Brown, Dr. David Savage and Dr. Anna Stears, and additional meetings to review findings are underway

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no published economic literature available on metreleptin in lipodystrophy patients.

Based on the results from this cost-effectiveness analysis, the ICER with PAS is a cost-effective use of NHS resources withjn the HST decision making criteria. This is due to a combination of large quantified QALY gain and unquantified direct and non-health benefits such as the broad impact on patients' and caregivers' lives (more detail in Section 14). Early intervention leads to substantial QALY gains and improved ICERs by preventing or slowing lipodystrophy's devastating progression. This is presented in an alternative model for base case patients with CGL starting metreleptin treatment from Age 1. The incremental QALYs are found to be 12.06, respectively. These gains are due to the high benefit of preventing emerging organ abnormalities and progression of the disease in these patients. There is also a substantial level of unquantified health and non-health benefits such as improvements in the QoL of carers/family of children and adults with lipodystrophy.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The model is based on patients from the US NIH, which represents a patient population that is different from the patients currently treated in the EAP in the UK. The US NIH patient data used in the model are more advanced patients than those currently treated in the EAP in England. Model sensitivities have illustrated that treatment in patients at less progressed stages of disease can provide greater QALY gains and high value and this is expected to be the case in England.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The model maximises transparency and flexibility as it follows real world observed patient level data and models individual patient's clinical experience and accruing costs and health benefits over time. Additionally, in extrapolating beyond the observed data, probabilities are used for each individual patient's development of organ abnormalities and resulting survival (and costs and utilities scaled accordingly) and in this sense the model leverages standard approaches from Markov models. Each individual patients can be thought of as a homogenous cohort in a Markov model with the overall results capturing the average across all patients. However, the model captures the heterogeneity of the underlying population and allows for history dependence in a manner that cannot be captured using a simpler structure. _ An alternate set of real world data, or different assumptions regarding the mix of

baseline characteristics, could be used to further explore the relationship between metreleptin cost-effectiveness and characteristics of the treated population.

A weakness of the model is the lack of existing literature to provide model inputs specific to metreleptin use in lipodystrophy patients. The economic model structure using individual patient data is not as widely used as more familiar Markov methods and there are limited previous submissions using this modelling approach. There are clear limitations in the data that can be used as inputs to the economic model, as might be expected with such a rare condition. These include the following:

- There is a lack of data on the costs associated with lipodystrophy and the consequences of LD such as multiple organ abnormalities. The SLR showed there were no useful published estimates, hence a structured questionnaire for use with clinical experts was developed to derive resource use estimates for the symptoms and complications of LD. Interviews were conducted with two leading clinical experts based at Cambridge University Hospital. Unfortunately, they were unable to provide highly meaningful estimates due to the very low numbers of patients treated and the great variation in patient profiles and resource utilisation across these patients, meaning it was difficult to provide typical, or 'on-average' estimates. The estimates in the model are based on a variety of sources, but are likely to underestimate the resource use reduction benefits of metreleptin as we have used conservative assumptions of cost in the absence of reliable data.

- The SLR indicated a lack of direct quality of life/PRO data for LD patients that could be useful for the economic model, or to assess the benefits of metreleptin, Hence there was a need to conduct a separate DCE in order to quantify the HRQL benefits of metreleptin vs. SoC. However, as mentioned it is likely that the DCE as conducted in the general public has underestimated the HRQL impact of LD on patients, and also has not captured impact on caregivers.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Several further analyses are planned or already underway to further enhance the robustness/completeness of these results:

1) Earlier initiation of metreleptin treatment, prior to the development of substantial organ abnormalities, may substantially extend life and improve quality of life. A preliminary analysis using the economic model suggests that QALY gains may be upward of 12.1. However, additional work could be done to more rigorously extend the existing framework to allow more rigorous modelling of the likely economic impact of early treatment initiation

2) The improvement metreleptin treatment patients experience with regard to organ abnormalities reflected in the current model is based on laboratory values for liver and kidney (and -in the scenario analysis- hypertension

resolution is used as a marker for improvement in heart abnormalities). However, the clinical trajectory of organ abnormalities included in the model (such as hepatomegaly and cardiomyopathy) can be more robustly documented with additional medical test results such as abdominal ultrasounds and echocardiograms. Additionally, further analysis of changes in the use of other medications may both add robustness to the current analysis of organ abnormality improvement and also support cost offsets not currently reflected in this model.

3) We acknowledge the patients from the NIH follow-up study may differ from patients seen in England. An effort is underway to collect data for patient in the United Kingdom participating in the early access programme (EAP) and these data can then be used with the existing model to directly estimate cost

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

Summary:

It is estimated that there would be 26 patients eligible for treatment with metreleptin in year 1 rising to 44 patients in year 5, across all lipodystrophy relevant to the metreleptin licence (GL and uncontrolled PL). The estimated uptake rate is 85% in year 1 (22 patients) rising to 90% in year 5 (40 patients). Adherence is assumed as 100% and discontinuation rate has been assumed as 0% due to such small discontinuation rates in the model in the first five years. Over five years, the cumulative budget impact of treating all patients with metreleptin 10mg dose and SoC, compared with treating only with SoC is estimated to be £133,045,965.00 at list price (£2,335 per 10mg dose vial) [BC1].

Additional vial sizes of metreleptin in 5.8mg and 3mg forms, with the intention of delivering a 5mg dose and a 2.5mg dose respectively, is anticipated to be available alongside the already submitted metreleptin 11.3mg vial (with the intention of administering a 10mg dose). These additional vial sizes will be submitted to the EU regulators as a variation to the expected licence, with a decision on the additional vials likely to be available three months following an EMA positive decision on the initial licence. The availability of three vial sizes will reduce wastage through allowing medical professionals to administer a more targeted and suitable dose for each patient, resulting in a significantly reduced average cost per patient per day. When considering the availability of all three vial sizes and expected doses per patient the cumulative five-year budget impact is £66,522,983.28 [BC2]. This scenario has been included as an additional budget impact, as base case number 2, as the availability of smaller vials significantly reduces drug wastage and hence the cost.

A simple price discount PAS has been applied for by Aegerion and is currently under review by PASLU. Should the intended PAS of a [redacted] simple price discount be approved, the corresponding cumulative budget impact over five years of treating the estimated number of patients with metreleptin 10mg dose and SoC, compared with treating only with SoC is estimated to [redacted][BC3]. This is based on a 10mg dose vial cost of [redacted]. The PAS discount will apply to all available doses at the same reduction rate should all vial sizes be approved by EU regulators. With the availability of the three vial sizes the cumulative budget impact, with PAS, of treating all expected patients over 5 years is estimated to be [redacted][BC4].

13.1 How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any

subgroups considered. Also present results for the subsequent 5 years.

There is a lack of published data available on the incidence and prevalence of lipodystrophy relevant to the metreleptin license, as supported by a conducted literature search which found limited epidemiology data. One study (Chiquette et al. 2017)(11) identified in the literature search was considered but was not deemed accurate or generalisable for a UK population and the anticipated metreleptin licence. The study conducted a search of five electronic medical record databases and literature searches to quantitively estimate the prevalence of LD but due to limitations of both searches the prevalence figures were not deemed robust or generalisable to current practice to determine England and Wales prevalence of LD. These study limitations included the search strategy used, the lack of data presented for LD subgroups (GL and uncontrolled PL), and uncertain assumptions used to obtain prevalence estimates. Given the availability of directly relevant and representative EAP data from a decade of metreleptin use in UK clinical practice, these figures were instead used for estimating patient numbers for the budget impact analysis.

An EAP has been provided for patients in Europe for 10 years, offering access to metreleptin on compassionate grounds for eligible lipodystrophy patients. As at October 2017, a total of 76 patients with GL and PL were receiving metreleptin treatment within the EAP across 10 countries. As part of the EAP, treatment with metreleptin in England is currently provided by a single centre at Addenbrooke's Hospital which is part of Cambridge University Hospitals (CUH) NHS Foundation Trust. Addenbrooke's hospital is the basis of the National Severe Insulin Resistance Service, as designated by NHS England, and provides a multidisciplinary NHS service for patients with severe insulin resistance and/or lipodystrophy from throughout England, supporting both adult and paediatric patients. The NHS service specification for this service includes the use of metreleptin. From this centre, there are currently (as at December 2017) 26 patients receiving metreleptin under the EAP, which equates to 9 patients with GL and 17 patients with uncontrolled PL. Of these patients, some may have initiated metreleptin a decade ago since the beginning of the EAP. As the EAP has been running for 10 years it is expected that the number of patients on the programme is a good indicator of the number of eligible patients in the UK.

The incidence of GL or uncontrolled PL has not been studied in the UK. Clinicians from Addenbrooke's Hospital in England who are involved in the UK EAP, have been consulted to provide an estimate of the number of new GL and uncontrolled PL patients, who present each year and would be eligible for metreleptin as per the licence. Based on expert clinical opinion, it is assumed that 6 new patients each year would be eligible for LD treatment (2 for GL and 4 for PL). To account for mortality in the budget impact, it has also been assumed that one patient with PL will die each year and one patient with GL will die every two years. Hence, these numbers have been combined and used to determine the uptake of LD. From EAP data and expert opinion the expected number of patients eligible over the next 5 years are presented in Table D58.

Table D58: Estimated eligible patient numbers for metreleptin

	Year 1	Year 2	Year 3	Year 4	Year 5
GL	9	11	12	14	15
PL	17	20	23	26	29
Total	26	31	35	40	44
Key: GL, generalised lipodystrophy; PL, partial lipodystrophy					

13.2 Describe the expected uptake of the technology and the changes in its demand over the next five years.

Based on the EAP data there has been an uptake of metreleptin over the past decade of 26 patients (9 GL, 17 PL) in the UK. Whilst it is unclear how many patients are eligible for metreleptin who have not started on treatment via the EAP, it is expected that the 26 patients currently treated will represent almost all of the total eligible patients in the UK. The team at Cambridge have over the past few years reached out to patients and clinicians to raise awareness of the service and EAP programme, having a frequent presence at relevant conferences with presentation slots. Hence, it is expected that the majority of lipodystrophy patients in the UK who would be eligible for treatment with metreleptin will be aware of the current services at Addenbrook's hospital available to patients. It is also assumed that NHS England intend to continue with this single centre of excellence approach, through Cambridge, and hence the nature of the availability of the product will not change following commercial availability.

As lipodystrophy patients do not currently have treatments specifically approved for the treatment of lipodystrophy, but would instead be prescribed treatments to manage the characteristics of the disease, it is expected that there would be a high uptake rate for metreleptin should it be supported by positive NICE guidance. As metreleptin will no longer be available through the EAP, it is anticipated that the majority of the 26 patients currently receiving treatment will remain on metreleptin under the responsibility of the NHS. It is likely that some patients will not continue metreleptin due to issues such as poor compliance but as there is no alternative treatment except SoC it is expected that the uptake rate of metreleptin will remain reasonably constant. The uptake rate has been assumed as 85% in year 1 rising to 90% in year 5, based on clinical expert opinion (Table D59). Discontinuation of metreleptin has been assumed as 0% in the first five years due to the discontinuation data used in the model resulting in negligible patients discontinuing over the first few years when paired with the small estimated patient numbers in the budget impact.

Table D59: Expected uptake rate of metreleptin over the next 5 years

Year 1	Year 2	Year 3	Year 4	Year 5
85%	85%	90%	90%	90%

13.3 In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).

Not applicable. There are no additional costs as these are already covered under the NHS Severe Insulin Resistance service.

13.4 Describe any estimates of resource savings associated with the use of the technology.

Not quantifiable. It is likely that patients on metreleptin will require less SoC treatment, and hence reduced resource use, but it is not possible to quantify these. Patients on metreleptin continue to receive SoC, so no treatment is explicitly displaced, but it is highly likely that the level of care associated with SoC will be reduced. However, it is difficult to quantify the SoC reduction for each patient and hence estimate the cost savings for patients receiving metreleptin. For example, metreleptin showed improvements in HbA1c and triglycerides in some patients which resulted in reductions or even discontinuation of the use of antidiabetic medications and/or lipid lowering medications, thus reducing the burden of diabetes and/or hypertriglyceridaemia management, both on the patient (e.g reducing pill burden) and the health service. There is also likely to be cost savings associated with a reduction in organ abnormality for each patient on metreleptin.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As noted in Section 13.4 it is expected that there will be resource savings, or redirection of resources, but these have not been possible to quantify.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Patients receiving metreleptin are expected to be able to improve their symptoms and quality of life to an extent where many would be able to return to work. School children with lipodystrophy are also affected but with a good response to metreleptin are expected to be able to complete school work with less barriers and difficulty due to the symptoms of their illness. These benefits would lead to more work productivity in the immediate future for adults and later in life for children who can manage their disease and have a normal working life as adults. Hence, there is a wider social benefit that is difficult to measure with the current data available.

13.7 What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?

Base case 1 (list price, single vial) [BC1]

At a list price of £2,335 per 10mg dose vial, the budget impact analysis is presented for all lipodystrophy patients relevant to the licence. This equates to annual medicine acquisition costs per patient for metreleptin on £852,858.75. All start-up costs required to administer metreleptin for each patient receiving metreleptin will be covered by Aegerion, hence supportive medicines costs of the treatment are expected to be zero. As SoC will be administered alongside metreleptin no medicine costs incurred as part of SoC are assumed to be displaced though requirements for anti-diabetic and lipid lowering medications have been shown to be reduced.

Based on the EAP patient numbers, expected incidence, and anticipated uptake rate, it is estimated that in Year 1 there will be 22 patients treated with metreleptin rising to 45 treated patients in Year 5. This equates to a net budget impact of £18,762,892.50 in Year 1 rising to £34,114,350.00 in Year 5. The net cumulative budget impact over years 1-5 is £133,045,965.00 at list price for all lipodystrophy patients. Results are presented in Table D60 for all lipodystrophy patients.

Table D60: **Overall lipodystrophy (GL and PL) budget impact analysis at list price (BC1)**

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition costs per patient per annum	£852,859	£852,859	£852,859	£852,859	£852,859
Supportive medicines cost per patient per annum	£0	£0	£0	£0	£0
Gross medicines costs per patient	£852,859	£852,859	£852,859	£852,859	£852,859
Displaced medicines cost*	£0	£0	£0	£0	£0
Net additional medicines cost per patient	£852,859	£852,859	£852,859	£852,859	£852,859
Eligible patient numbers	26	31	35	40	44
Uptake rate	85%	85%	90%	90%	90%
Number of patients treated	**22**	**26**	**32**	**36**	**40**
Other savings / costs*	£0	£0	£0	£0	£0
Net budget impact	**£18,762,893**	**£22,174,328**	**£27,291,480**	**£30,702,915**	**£34,114,350**
Cumulative net budget impact	**£18,762,893**	**£40,937,220**	**£68,228,700**	**£98,931,615**	**£133,045,965**
*cost savings and displaced medicine costs associated with the introduction of metreleptin are likely but have not been quantified so are assumed as zero. Please note figures have been rounded to the nearest whole £					

Base case 2 (list price, multiple vials) [BC2]

With the introduction to the market of additional vial sizes of metreleptin of 5mg and 2.5mg doses there will be significantly less drug wastage. Metreleptin follows linear pricing across vial sizes with the list price of the 5mg dose vial being £1,167.50 and price of a 2.5mg dose vial of £583.80. It is expected that these alternative vial sizes will be approved by EU regulatory three months after the 10mg dose vial and will offer clinicians more options for treating patients, which will allow them to prescribe presentations more suited to the patient's daily dose. The budget impact with all three vial sizes available is based on the proportion of patients in the EAP data currently receiving each vial size. The majority of patients (69.23%) receive the 5mg dose with less patients receiving the 10mg dose and 3mg dose. The proportion of patients receiving each vial size, based on EAP data, is shown in **Table D61**. It is important to note that very few patients receive the 10mg dose vial (n=3) which is currently the basis of the base case budget impact and economic analysis, hence should the alternative vial sizes be approved this scenario analysis will be much more representative of current clinical practice in England than the base case using 10mg.

Table D61: Summary of the number of EAP patients currently receiving each vial size (as at December 2017)

	11.3mg vial (10mg dose)	5.8mg vial (5mg dose)	3mg vial (2.5mg dose)
Proportion of EAP patients receiving each vial size	11.54% (n=3)	69.23% (n=18)	19.23% (n=5)
Key: mg, milligram; n, number			

Assuming all three vials are available, and the proportion of patients receiving each vial size reflects the EAP data, the annual cost of treating one patient with lipodystrophy is £434,633.45. This results in a net budget impact of £9,561,935.90 in Year 1 rising to £17,385,338.00 in Year 5. The net cumulative budget impact over years 1-5 is £67,802,818.20 at list price for all lipodystrophy patients. The budget impact for this scenario is presented in Table D62.

Table D62: Overall lipodystrophy (GL and PL) budget impact analysis at list price – scenario with all vial sizes available (list price) (BC2)

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition costs per patient per annum	£434,633	£434,633	£434,633	£434,633	£434,633
Supportive medicines cost per patient per annum*	£0	£0	£0	£0	£0
Gross medicines costs per patient	£434,633	£434,633	£434,633	£434,633	£434,633
Displaced medicines cost*	£0	£0	£0	£0	£0
Net additional medicines cost per patient	£434,633	£434,633	£434,633	£434,633	£434,633
Eligible patient numbers	26	31	35	40	44
Uptake rate	85%	85%	90%	90%	90%

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated	**22**	**26**	**32**	**36**	**40**
Other savings / costs	£0	£0	£0	£0	£0
Net budget impact	**£9,561,936**	**£11,300,470**	**£13,908,270**	**£15,646,804**	**£17,385,338**
Cumulative net budget impact	**£9,561,936**	**£20,862,406**	**£34,770,676**	**£50,417,480**	**£67,802,818**
*cost savings and displaced medicine costs associated with the introduction of metreleptin are likely but have not been quantified so are assumed as zero. Please note figures have been rounded to the nearest whole £					

An additional point to note is that the budget impact analysis for multiple vials is based on the data provided but it may be that there could be additional savings if clinicians choose the vial sizes fitted to the patient dose requirement. For example a patient on 5-7.5mg would result in a lower budget impact should the patient be prescribed a 5mg and 2.5mg dose vial. It is unclear if this is currently happening in clinical practice.

Base case 3 (PAS price, single vial) [BC3]

As a simple PAS discount is currently being submitted to PASAG, results are presented below at the anticipated PAS price of £[redacted] per 11.3mg vial (10mg dose) following a successful application. This equates to treatment costs with metreleptin of £[redacted] per patient per annum. Results are presented in **Table D63** for all lipodystrophy at PAS price.

At PAS price, it is estimated that the net budget impact will be £[redacted] in Year 1 rising to £[redacted] in Year 5. The net cumulative budget impact over years 1-5 is £[redacted] for all lipodystrophy patients.

Table D63: **Overall lipodystrophy (GL and PL) budget impact analysis at PAS price**

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition costs per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supportive medicines cost per patient per annum	£0	£0	£0	£0	£0
Gross medicines costs per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost*	£0	£0	£0	£0	£0
Net additional medicines cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patient numbers	26	31	35	40	44
Uptake rate	85%	85%	90%	90%	90%
Number of patients treated	**22**	**26**	**32**	**36**	**40**
Other savings / costs*	£0	£0	£0	£0	£0
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Cumulative net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*cost savings and displaced medicine costs associated with the introduction of metreleptin are likely but have not been quantified so are assumed as zero. Please note figures have been rounded to the nearest whole £					

Base case 4 (PAS price, multiple vials) [BC4]

As noted earlier, there are three vial sizes of metreleptin available (11.3mg vial, 5.8mg vial, and 3mg vial) from Aegerion. Should all three vial sizes receive EU regulatory approval the budget impact will be much lower than all patients receiving a daily vial of 11.3mg as generally this is a much higher dose than patients require and so there is a lot of drug wastage. The budget impact, with PAS, for this scenario where all vials are available is provided in Table D64. The budget impact considers that 11.54% patients receive the 10mg dose vial, 69.23% patients receive the 5mg dose vial, and 19.23% patients receive the 2.5mg dose vial, as per the EAP December 2017 data. At PAS price, it is estimated that the net budget impact will be £[redacted] in Year 1 rising to £[redacted] in Year 5. The net cumulative budget impact over years 1-5 is £[redacted] for all lipodystrophy patients.

Table D64: Overall lipodystrophy (GL and PL) budget impact analysis at list price – scenario with all vial sizes available (PAS price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition costs per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supportive medicines cost per patient per annum	£0	£0	£0	£0	£0
Gross medicines costs per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost*	£0	£0	£0	£0	£0
Net additional medicines cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patient numbers	26	31	35	40	44
Uptake rate	85%	85%	90%	90%	90%
Number of patients treated	**22**	**26**	**32**	**36**	**40**
Other savings / costs*	£0	£0	£0	£0	£0
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*cost savings and displaced medicine costs associated with the introduction of metreleptin are likely but have not been quantified so are assumed as zero. Please note figures have been rounded to the nearest whole £					

13.8 Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).

There is a lack of prevalence and incidence data for the UK so estimates have been assumed based on the EAP data and expert clinician opinion (Section 13.1 details the limitations of the available data). However, given the context of the EAP it is expected that this is likely to provide a more accurate and relevant estimate representing clinical practice in England and Wales and the prevalence of disease. It is also important to note that published literature generally refers to all GL or PL but the licence is only relevant to the uncontrolled PL population. Incidence has been estimated from experts with experience in treating lipodystrophy patients both on and off the EAP. Estimating the uptake rate of metreleptin is difficult as it is expected that the majority of patients currently on treatment are expected to continue treatment, with few new patients expected to be eligible for treatment given the ultra-orphan nature of lipodystrophy. There is no known data available that could be used to obtain an uptake rate hence clinical opinion has been used. The limitations regarding the availability of data affect the budget impact analysis as small variations in the number of patients treated each year with metreleptin could have a significant effect on overall budget impact. Conversely, the number of patients eligible each year and those up taking treatment with metreleptin could be overestimated, and hence be overstating the true budget impact analysis. Another limitation is that additional vial sizes of metreleptin will be submitted on a variation following approval of the 10mg dose vial which has limited the budget impact analysis base case to consider the 10mg dose vial only for all patients, despite this not being the most common dose used in current clinical practice in England. Based on the metreleptin EAP data it appears that of the three vial sizes available the 10mg dose vial is the least used, hence the budget impact analysis base case is likely to be an overestimation of current clinical practice. For this reason, a scenario analysis considering all vial sizes was included. However, it is unclear how clinicians are currently administering certain doses and it could be that the budget impact is lowered again for those patients on 5-7.5mg should the patient be prescribed a 5mg and 2.5mg dose vial. It is unclear if this is currently happening in clinical practice hence the more conservative approach was taken using data directly from the EAP on which vial sizes are currently being used rather than making any further assumptions.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.

The majority of the cost and health outcomes relevant to the decision problem are expected to be captured within the economic analyses presented here, with the costs of treatment and management of LD primarily borne by the NHS and PSS. However, the work loss associated with LD can be quite substantial. Most patients are affected from birth due to genetic/familial disease, with symptoms such as hyperphagia and organ abnormalities manifesting in childhood, and therefore carers/familes are also heavily impacted. Patients with hyperphagia are highly constrained by food access issues, affecting many aspects of their daily lives including attending school and work. Carers may need to provide 24/7 supervision, especially as patients may also consume inappropriate or non-food items. Other symptoms such as fatigue, frequent infection/illness, anxiety/depression, as well as the management of severe metabolic abnormalities including hypertriglyceridaemia, insulin resistance, and/or diabetes and their co-morbidities, can also lead to impaired or complete inability to work or attend school.

Of the 114 patients treated with metreleptin at the NIH, 35% had one caregiver, typically their mother, not working or only working part time to support them due to their disease. (45) Following metreleptin initiation, only 7% (or a 80% reduction) of

these patients had a caregiver not working or only working part time. The work-loss impact is also very significant on patients themselves, both due to the impaired ability to work as adults, as well as due to impaired schooling as children. For example, of 50 adult patients treated with metreleptin at NIH, 48% did not work (or go to university), with at least 1/3 due to lipodystrophy. In addition among 64 non-adult patients treated with metreleptin, 59.4% had impaired school attendance.

Overall, this is a population for whom an effective therapy has the potential for a profound positive effect on lifestyle opportunities and QoL of patients and carers, including attending work and school.

14.2 List the costs (or cost savings) to government bodies other than the NHS.

Due to the impact of LD on young patients, the need for additional support at school may be significant, but is unquantifiable at present. In England (and the rest of the UK), the local authority is under a duty to ensure that a child with medical conditions, in terms of both physical and mental health, receives as normal an education as possible to achieve their academic potential.(104) Schools, local authorities, health professionals, commissioners and other support services work together to ensure that children with medical conditions receive a full education. In some cases this requires flexibility and involves, for example, programmes of study that rely on part-time attendance at school in combination with alternative provision arranged by the local authority. Therefore, additional resources and costs may be required from the local authority with regards to education and social services. Other costs may include disability and other welfare payments due to not being able to work.

14.3 List the costs borne by patients that are not reimbursed by the NHS.

Patients with LD need to manage living with type 2 diabetes and the subsequent complications at a very young age. The indirect costs of diabetes in UK have been estimated to be considerably higher than the direct costs and many relate to a cost to the individual with diabetes or their carers.(105) Another study in the UK reported on individual earnings lost by patients with type 2 diabetes (n=653) and carers (n=253) aged <65 years based on 1998 values.(106) Mean lost earnings were estimated at £869 (S.D. £4109) per patient and £1300 (S.D. £4093) per carer; for the sub-set of respondents who actually lost earnings, the mean levels were £13841 (S.D. £9551) and £10960 (£6002), respectively. A strong association was found between patients' loss of earnings and the presence of diabetic complications (P<0.001). The lost earnings in LD patients may be even more significant in LD patients given the early age at which they can experience complications when not managed effectively.Patients with LD need to manage living with type 2 diabetes and the subsequent complications at a very young age. The indirect costs of diabetes in UK have been estimated to be considerably higher than the direct costs and many relate to a cost to the individual with diabetes or their carers.(105) Another study in the UK reported on individual earnings lost by patients with type 2 diabetes (n=653) and carers (n=253) aged <65 years based on 1998 values.(106) Mean lost earnings were

estimated at £869 (S.D. £4109) per patient and £1300 (S.D. £4093) per carer; for the sub-set of respondents who actually lost earnings, the mean levels were £13841 (S.D. £9551) and £10960 (£6002), respectively. A strong association was found between patients' loss of earnings and the presence of diabetic complications ($P<0.001$). The lost earnings in LD patients may be even more significant in LD patients given the early age at which they can experience complications when not managed effectively.

Other costs incurred by patients and carers include transport to the hospital. It has been estimated that about 20% of LD patients (lower bound estimate) will be hospitalised in a given year, with more than 5 hospitalisations per year observed in some patients (Data on file).

Other potential costs may include fertility treatment and cosmetic treatment, which are not always reimbursed by the NHS.

It is anticipated that effective management of LD, including treatment with metreleptin when needed, helps to mitigate these costs.

With regard to metreleptin treatment, LD patients who are referred to the specialist centre at Addenbrooke's have travel costs to Cambridge, which can also include overnight accommodation for those traveling further. Patients would typically need to visit the clinic twice a year. Otherwise, metreleptin is self-administered at home and patients are reviewed by their local team and/or GP in between appointments at the specialist centre.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

Surveys from EURORDIS-Rare Disease Europe and from Rare Diseases UK have described how the time burden is substantial for a majority of people living with a rare disease and their carers, especially because of daily care and care coordination, with 42% spending more than 2 hours a day on caring.(107, 108) This time burden falls heavily on women, who are often the main carers.(107, 108) This time burden falls heavily on women, who are often the main carers. As described in 14.1, of the 114 patients treated with metreleptin at the NIH, 35% had one caregiver, typically their mother, not working or only working part time to support them due to their disease. Following metreleptin initiation, only 7% (an 80% reduction) of these patients had a caregiver not working or only working part time. Aergerion are currently conducting market research in England to further help understand the impact on carers in more detail. While data is currently lacking for estimates of time spent by family members of providing care for LD patients, patient interviews suggest the burden is significant in some cases. In particular, some children with hyperphagia require constant supervision to try to manage their eating habits, especially as they may eat inappropriate and/or non-food items (see Section 7.1).

14.5 Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or

disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.

To support the development of metreleptin, Aegerion, despite its limited resources as a small biotech company, has engaged in a comprehensive evidence generation programme to strengthen the evidence base on the understanding of LD and the clinical effectiveness of metreleptin. Key recent contributions include and are not limited to:

- Assessing the organ abnormality burden and its progression, and mortality
- Assessing the burden of disease and performance of metreleptin in LD patients enrolled in the EAP, including patients treated in England at Addenbrooke's
- Characterising the broad and profound impact of metreleptin on LD patients beyond HbA1c and triglycerides, but also organ abnormalities, mortality, hyperphagia, reproductive dysfunction, work/school impact on patients and their carers
- Assessing patient preferences vis a vis LD attributes

Aegerion is committed to continue to support such evidence generation, and hopes that based on its availability in the UK, it will be able to continue to pursue in the future:

- A more comprehensive review of the burden of disease and performance of metreleptin in UK and other EAP patients
- A registry of UK lipodystrophy patients capturing their experience prior and post metreleptin treatment

This is particularly viable in the context of a centre of excellence at Addenbrooke's, Cambridge, where the clinicians are actively engaged in research, education and raising the profile of LD as a clinical problem in order to improve access to optimal care for affected patients.(109)

14.6 Describe the anticipated impact of the technology on innovation in the UK.

As described in the Department of Health's UK Strategy for Rare Diseases, the UK is a trusted and respected leader in research into rare diseases and that by improving the link between research and services for patients a culture of innovation will be promoted.(110) In-line with this, as part of the EAP, metreleptin has been used and its effectiveness studied for over 10 years in patients at Addenbrooke's, Cambridge, with the aim of improving the lives of LD patients and their families, as well as providing education and helping to raise the profile of this little-known disease.

Currently, metreleptin is the only therapy specifically for LD, acting on the underlying cause of leptin deficiency, and therefore represents an important innovation in the management of LD. The major therapeutic approaches in patients with LD are those used in the related metabolic disorder, and include diet, insulin, and oral anti-diabetic and lipid lowering agents. The major problem with this approach is that the metabolic disturbance is severe and does not respond well to these conventional approaches.(63)

In contrast, metreleptin acts on an underlying cause of GL and PL complications, i.e., leptin deficiency. Metreleptin is associated with significant benefits over standard of care for which treatment in ineffective or there are no treatment options available: it is effective in controlling metabolic parameters (HbA1c and triglycerides) that have not responded to conventional therapy;(9, 10, 56, 61, 66) it can significantly improve hepatic steatosis and NASH;(57, 58, 64) it is associated with significant improvements in measures of satiety and decreases in food intake;(54, 55) it has been shown to halt or in some cases reverse organ abnormality associated with LD; female patients experiencing infertility and other reproductive dysfunction (e.g., PCOS) have experienced improvement and successful pregnancy following initiation of metreleptin; and improvements in the physical appearance of LD patients have also been reported.(56, 61, 62) Overall, metreleptin represents an important step-change in the management of LD patients.

Furthermore, the availability of metreleptin in the UK will help foster investments in drug innovation for UK patients in currently underserved rare disease areas.

14.7 Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.

The metreleptin EAP is allowing for collection of data in a cohort of patients in Europe, with a total of 76 patients currently receiving treatment in 10 countries. including 26 in the UK, who are being treated at Addenbrooke's. Data are being collected to match key clinical trial endpoints (e.g., triglycerides, HbA1c) and also covering a wide array of additional disease characteristics such as hyperphagia, female reproductive dysfunction, and organ systems related abnormalities. Data from an interim analysis is expected in Q1/Q2 2018. Going forwards data can continue to be collected on treated patients, which is particularly viable in the context of a centre of excellence at Addenbrooke's, Cambridge.

In addition, Aegerion has offered to the EMA that they will conduct a disease registry as part of the Risk Management Plan for metreleptin in Europe. This registry would be open in principle to all patients within the EMA with GL and PL, who are treated with metreleptin or with symptomatic treatment alone and would include assessments of safety and efficacy. The precise format of this registry with respect to number of patients and duration is under discussion with the EMA. In the US, Aegerion are also running a product registry called MEASURE.

14.8 Describe any plans on how the clinical effectiveness of the technology will be reviewed.

Data will continue to be collected at Addenbrooke's, providing appropriate real world evidence of relevant outcomes in clinical practice of LD patients receiving metreleptin, in order to review its on-going clinical effectiveness.

14.9 What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?

Metreleptin has been available for more than 10 years in the UK through the EAP and thus that there is already a lot of expertise within the NHS to support the safe and effective use of this treatment. Patients are trained by healthcare professionals on the proper subcutaneous injection technique, following which metreleptin is administered at home by the patient or carer.

14.10 Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?

It is anticipated that no additional facilities, technology or infrastructure will be required for the introduction of metreleptin on the NHS in England. Metreleptin will be prescribed and monitored within the existing specialist service at Addenbrooke's. Currently, patients receiving metreleptin are reviewed on a regular basis (usually 6-monthly) as indicated by their clinical progress.(8) Otherwise, the service maintains contact with local specialists and GPs to provide advice as required. Metreleptin is self-administered daily at home by the patients or carers following initial training by healthcare professionals. Potential implementation of commercial/post-marketing neutralising antibody testing in the EU, possibly in patients with severe or serious infections, is being discussed with the CHMP, but is currently unresolved.

Section F - Managed Access Arrangements **(please see sections 55-59 of the HST methods guide on MAAs)**

15 Managed Access Arrangement

15.1 Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA

Aegerion are happy to work with NHSE, NICE and the patient group to develop a MAA if appropriate & needed, Aegerion felt it would be beneficial for all to first understand any feedback provided by the committee following review of this document

15.2 Describe the specifics of the MAA proposal, including:

- The duration of the arrangement, with a rationale
- What evidence will be collected to reduce uncertainty
- How this evidence will be collected and analysed
- The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA
- Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)
- Funding arrangement, including any commercial proposals or financial risk management plans
- The roles and responsibilities of clinical and patient groups during the MAA
- What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed

15.3 Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA

Not applicable at the current time.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

17.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Studies were identified by searches of the following electronic databases:

- Ovid MEDLINE and MEDLINE In-Process
- Ovid EMBASE
- Database of Abstracts and Review of Effects
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews
    - Health Technology Assessment Database
- National Health Service (NHS) Economic Evaluation Database (EED)

17.1.2 The date on which the search was conducted.

The search was conducted on 10th March 2017.

17.1.3 The date span of the search.

There were no restrictions on date of publication.

17.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> March 10, 2017

Search Strategy:

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1 exp Lipodystrophy/ or exp HIV-Associated Lipodystrophy Syndrome/ or exp Lipodystrophy, Familial Partial/ or exp Lipodystrophy, Congenital Generalized/ (4544)

2 lawrence syndrome$.tw. (15)

3 *Endocrine System Diseases/ (6305)

4 (lipodystrop$ or lipid dystrop$ or lipidome$ or lipoatroph$).tw. (6083)

5 (kobberling or koebberling).tw. (18)

6 ((metabolic skin or connective tissue or lipid metabolism) adj1 (disease$ or disorder$)).ti,ab. (12048)

7 or/1-6 (25691)

8 (metreleptin or myalept or leptin).af. (32091)

9 7 and 8 (513)

10 (animals not (humans and animals)).sh. (4326645)

11 9 not 10 (441)

****

Database: Embase <1974 to 2017 March 10>

Search Strategy:

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1 exp congenital generalized lipodystrophy/ or exp intestine lipodystrophy/ or exp lipodystrophy/ or exp HIV associated lipodystrophy/ or exp familial partial lipodystrophy/ (10860)

2 lawrence syndrome$.tw. (16)

3 *endocrine disease/ (6807)

4 (lipodystrop$ or lipid dystrop$).tw. (5422)

5 lipoatroph$.tw. (1993)

6 (kobberling or koebberling).tw. (20)

7 ((metabolic skin or connective tissue or lipid metabolism) adj1 (disease$ or disorder$)).ti,ab. (17679)

8 or/1-7 (37059)

9 (metreleptin or myalept or leptin).af. (50338)

10 8 and 9 (991)

11 letter.pt. (980178)

12 editorial.pt. (535816)

13 10 not (or/11-12) (947)

14 limit 13 to human (781)

Search Name: **The Cochrane Library**

Date Run: **12/03/17**

Description:

ID	Search	Hits
#1	MeSH descriptor: [Lipodystrophy] explode all trees	180
#2	Lipodystrophy:ti,ab,kw (Word variations have been searched)	285
#3	MeSH descriptor: [Endocrine System Diseases] explode all trees	28665
#4	MeSH descriptor: [Lipid Metabolism Disorders] explode all trees	5887
#5	MeSH descriptor: [Skin Diseases, Metabolic] explode all trees	185
#6	MeSH descriptor: [Metabolic Diseases] explode all trees	32683

#7 MeSH descriptor: [Nutritional and Metabolic Diseases] explode all trees 42727

#8 (metreleptin or myalept or leptin):ti,ab,kw (Word variations have been searched) 2001

#9 MeSH descriptor: [Leptin] explode all trees 876

#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101#1 (111-#7) 53101

#11 (75-#9) 2001

#12 (83-#11) **753**

(Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2017: 0

Database of Abstracts of Reviews of Effect (DARE): Issue 2 of 4: 3

Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2017: 749

Health Technology Assessment Database (HTA): Issue 4 of 4: 1)

17.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Key international HTA websites were searched for relevant HTAs including: NICE; SMC; The National Healthcare Institute in the Netherlands; Belgium Healthcare Knowledge Centre; IQWiG, Germany

Searches for grey literature were undertaken to capture evidence presented at relevant conferences that have not yet been published as full-text journal articles. Searches for grey literature were undertaken to capture evidence presented at relevant conferences that have not yet been published as full-text journal articles. These searches were limited to conferences within the past four years, as any high-quality studies should have been reported as journal articles within this time. Any abstracts older than this were excluded in the screening stage. Only conferences with freely available and searchable abstracts were considered.

The following conference websites were searched: International Conference on Metabolic Syndrome; International Conference on Endocrinology; Endocrine Society Conference; American Diabetes Association; Annual Congress on Endocrine Disorders and Therapies; European Association for the Study of Diabetes; European Conference of Endocrinology; European Society for Paediatric Endocrinology; Paediatric Endocrine Society; EndoBridge.

On-going trials were searched for using Clinicaltrials.gov register (clinicaltrials.gov) and the World Health Organization trial register (apps.who.int/trialsearch).

In addition, reference lists of studies identified from the electronic search and any recent systematic reviews and/or meta-analyses were screened.

Finally, internal sources at Aegerion Pharmaceuticals associated with ongoing clinical studies (e.g. natural history study in LD, NIH sub-studies, early access

programme related studies) and unpublished clinical study reports were to be assessed.

17.1.6 The inclusion and exclusion criteria.

See Section 9.2.1 for the inclusion and exclusion criteria

17.1.7 The data abstraction strategy.

The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. (112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. (112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review

researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. (112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. (112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher. The process of study selection was made according to specifications in the Protocol.(112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. (112) All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second researcher.

17.2 Appendix 2: Search strategy for adverse events

The search strategy for adverse events is the same as for clinical evidence (Section 17.1).

17.3 Appendix 3: Search strategy for economic evidence

The following information should be provided.

17.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Studies were identified by searches of the following electronic databases:

- Ovid MEDLINE and MEDLINE In-Process
- Ovid EMBASE
- EconLit
- Database of Abstracts and Review of Effects
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews
    - Health Technology Assessment Database
    - National Health Service (NHS) Economic Evaluation Database (EED)

17.3.2 The date on which the search was conducted.

Electronic searches were conducted between during February 2017 and up to 7th March 2017.

17.3.3 The date span of the search.

Papers published from 2006 (inclusive) to January 2017 were considered; any studies published prior to 2006 were excluded. Only conference abstracts published within the last four years (January 2013 to January 2017, inclusive) were considered. Letters, newsletters, bulletins, editorials, commentaries and fact sheets were excluded.

17.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Database: Embase <1974 to 2017 March 06>
Search Strategy:

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1 exp lipodystrophy/ or exp HIV associated lipodystrophy/ or exp intestine lipodystrophy/ or exp familial partial lipodystrophy/ or exp congenital generalized lipodystrophy/ (10852)
2 lipodystrophy.tw. (4996)
3 lawrence syndrome$.tw. (16)
4 *endocrine disease/ (6803)
5 (kobberling or koebberling).tw. (20)
6 lipoatrophy.tw. (1700)
7 lipohypertrophy.tw. (387)
8 ((metabolic skin or connective tissue or lipid metabolism) adj1 (disease$ or disorder$)).ti,ab. (17654)
9 ((nutritional and metabolic) adj1 (disease$ or disorder$)).ti,ab. (2993)

10 health economics/ or economics/ (257244)
11 exp "cost utility analysis"/ or exp "hospitalization cost"/ or exp "cost effectiveness analysis"/ or exp "drug cost"/ or exp "health care cost"/ or exp "cost control"/ or exp "program cost effectiveness"/ or exp "cost of reproduction"/ or exp "energy cost"/ or exp "cost benefit analysis"/ or exp "cost minimization analysis"/ or exp "cost"/ or exp "hospital cost"/ or exp "cost of illness"/ (494292)
12 (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$ or price$ or pricing).tw. (819423)
13 (cost$ adj2 (effective$ or consequence$ or utilit$ or benefit$ or variable$ or minimi$ or analy$ or estimate$ or unit$ or outcome or outcomes)).ti,ab. (192272)
14 (decision adj2 model).tw. (7763)
15 ((resource$ adj1 allocat$) or (productivity adj1 loss) or absenteeism$ or (indirect adj1 cost$)).tw. (23313)
16 exp quality adjusted life year/ (19993)
17 *patient satisfaction/ (20650)
18 (markov or health utilit$ or hrql or hrqol or disabilit$).tw. (237196)
19 quality adjusted life.ti,ab. (13666)
20 disability adjusted life.ti,ab. (2573)
21 (qaly$ or qald* or qale* or qtime* or life year or life years).ti,ab. (23118)
22 *"quality of life"/ (96052)
23 budget impact.ti,ab. (2284)
24 or/1-9 (39834)
25 or/10-23 (1485799)
26 24 and 25 (1496)
27 letter.pt. (979701)
28 editorial.pt. (535456)
29 26 not (or/27-28) (1466)
30 limit 29 to human (1331)

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Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 exp Lipodystrophy/ or exp HIV-Associated Lipodystrophy Syndrome/ or exp Lipodystrophy, Familial Partial/ or exp Lipodystrophy, Congenital Generalized/ (4517)
2 lipodystrophy.tw. (4009)
3 lawrence syndrome$.tw. (15)
4 *Endocrine System Diseases/ (6280)
5 (kobberling or koebberling).tw. (18)
6 lipoatrophy.tw. (1347)
7 lipohypertrophy.tw. (251)
8 ((metabolic skin or connective tissue or lipid metabolism) adj1 (disease$ or disorder$)).ti,ab. (11916)
9 ((nutritional and metabolic) adj1 (disease$ or disorder$)).ti,ab. (2033)
10 exp Economics/ (541678)
11 exp "Costs and Cost Analysis"/ or exp Cost-Benefit Analysis/ or exp "Cost of Illness"/ or exp Health Care Costs/ (205716)
12 (pharmacoeconomic$ or pharmaco-economic$ or cost$ or economic$ or price$ or pricing).tw. (638175)
13 (cost$ adj2 (effective$ or consequence$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)).ti,ab,kw. (134280)
14 budget impact.ti,ab. (900)
15 (decision adj2 model).tw. (5262)
16 ((resource$ adj1 allocat$) or (productivity adj1 loss) or absenteeism$ or (indirect adj1 cost$)).tw. (17536)
17 exp quality-adjusted life years/ (9115)
18 exp Patient Satisfaction/ (74125)
19 (markov or health utilit$ or hrql or hrqol or disabilit$).tw. (173582)
20 quality adjusted life.ti,ab,kf. (9292)
21 disability adjusted life.ti,ab,kw. (2137)
22 (qaly$ or qald* or qale* or qtime* or life year or life years).ti,ab,kf. (14928)
23 *"Quality of Life"/ (67587)
24 or/1-9 (26698)
25 or/10-23 (1283745)
26 24 and 25 (767)

****

Database: The Cochrane Library

Date Run: 07/03/17
Search Strategy:

ID	Search	Hits
#1	Lipodystrophy:ti,ab,kw (Word variations have been searched)	285
#2	MeSH descriptor: [Lipodystrophy] explode all trees	180
#3	#1 or #2	285

- Database of Abstracts of Reviews of Effect (DARE): Issue 2 of 4: 6
- Health Technology Assessment Database (HTA): Issue 4 of 4: 4
- NHS Economic Evaluation Database (NHSEED): Issue 2 of 4: 1

****
Results:
Total number of references: 2109

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Key international HTA websites were searched for relevant HTAs including: NICE; SMC; The National Healthcare Institute in the Netherlands; Belgium Healthcare Knowledge Centre; IQWiG, Germany.

Searches for grey literature were undertaken to capture evidence presented at relevant conferences that have not yet been published as full-text journal articles. Searches for grey literature were undertaken to capture evidence presented at relevant conferences that have not yet been published as full-text journal articles. These searches were limited to conferences within the past four years, as any high-quality studies should have been reported as journal articles within this time. Any abstracts older than this were excluded in the screening stage. Only conferences with freely available and searchable abstracts were considered.

The following conference websites were searched: International Society for Pharmacoeconomics and Outcomes Research; International Conference on Metabolic Syndrome; International Conference on Endocrinology; Endocrine Society Conference; American Diabetes Association; Annual Congress on Endocrine Disorders and Therapies; European Association for the Study of Diabetes; European Conference of Endocrinology; European Society for Paediatric Endocrinology; Paediatric Endocrine Society; EndoBridge.

In addition, reference lists of studies identified from the electronic search and any recent systematic reviews and/or meta-analyses were screened.

17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

17.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline

- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The search strategy for resource identification, measurement and valuation is the same as for economic evidence (Section 17.3)

17.4.2 The date on which the search was conducted.

The search strategy for resource identification, measurement and valuation is the same as for economic evidence (Section 17.3)

17.4.3 The date span of the search.

The search strategy for resource identification, measurement and valuation is the same as for economic evidence (Section 17.3)

17.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategy for resource identification, measurement and valuation is the same as for economic evidence (Section 17.3)

17.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The search strategy for resource identification, measurement and valuation is the same as for economic evidence (Section 17.3)

17.4.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria applied to the papers identified for the cost and resource use review are summarised in Table 65.

Table 65: Inclusion and exclusion criteria for the cost and resource use component of the SLR

	Inclusion criteria	Exclusion criteria
Population	Patients with congenital or generalised lipodystrophy Patients with familial or partial lipodystrophy HIV-associated lipodystrophy in which costs/HRQL were presented specific to lipodystrophy	Healthy volunteers Animal studies Patients with HIV in which lipodystrophy was a side effect of treatment and costs/HRQL were not presented specific to lipodystrophy.

	Patients with rare lipodystrophy syndromes (e.g. Donohue syndrome, mandibuloacral dysplasia (type A and type B) and Wiedemann Rautenstrauch syndrome) Lipodystrophy secondary to drug administration (insulin growth hormone, steroids, antibiotics and vaccinations) Lipodystrophy secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections Patients with lipoatrophy or lipohypertrophy if considered a subset of lipodystrophy	Patients with lipoatrophy or lipohypertrophy specifically with no mention of lipodystrophy.
Interventions	Studies not filtered by intervention	
Outcomes	Unit costs, total costs, resource use associated with intervention or resource use associated with lipodystrophy and/or metabolic complication	
Study types	Studies including (but not restricted to): cost and resource use studies, burden of illness studies, HRQL studies, utility studies, economic evaluations including: • Cost-consequence • Cost-minimisation • Cost-effectiveness • Cost-utility • Cost benefit • Budget impact Ongoing studies available internally at Aegerion Pharmaceuticals (unpublished)	Systematic literature reviews Clinical only studies (these were cross checked with studies identified in the clinical SLR)
Publication types	Journal articles, reports and summaries Papers published from 2006 (inclusive) to January 2017 Conference abstracts published within the last four years (January 2013-January 2017, inclusive)	Letters, newsletters, bulletins and fact sheets Editorials or commentaries Papers published before 2006 Conference abstracts published before 2013
Other	Studies were not filtered based on language Studies considering data from UK, France, Spain, Italy, Germany, Netherlands, Belgium and Turkey	Studies considering data from countries other than the UK, France, Spain, Italy, Germany, Netherlands, Belgium and Turkey
Key: HIV, human immunodeficiency virus; HRQL, health related quality of life; SLR, systematic literature review; UK, United Kingdom		

17.4.7 The data abstraction strategy.

All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables

by a researcher and verified against the original source paper by a second researcher.

If study duplication was suspected then author names, location and setting, methods and results used were cross-examined and noted within the data extraction table. Furthermore, if a paper presented results from a secondary follow up the location and setting, source of data and results were cross-examined with the primary paper and noted within the data extraction table. If no additional information was present, no data were extracted from the secondary papers.

17.5 Appendix 5: Utility Study

17.5.1 Background

Lipodystrophy is a rare condition associated with partially or fully absent subcutaneous adipose tissue (body fat under the skin). As a result, fat accumulates in nonadipose tissues, which leads to cosmetic irregularities and, more importantly, to metabolic abnormalities such as insulin resistance, diabetes, hypertriglyceridemia, and further complications and comorbidities such as acute pancreatitis, hepatic steatosis, cirrhosis, cardiovascular disease, diabetic-associated end stage renal disease, and other complications of diabetes (5, 21, 112, 113). In addition, lipodystrophy patients experience high rates of hyperphagia, characterised by constant and insatiable hunger, and female reproductive dysfunction.

Due to a lack of adipocytes associated with lipodystrophy, a marked reduction in leptin levels is often observed in patients (3). Leptin is a hormone produced by adipose tissue that regulates several metabolic processes including glucose homeostasis, insulin sensitivity, and fatty acid oxidation (114). Leptin deficiency observed in lipodystrophy leads to the development of numerous metabolic abnormalities. Therefore, restoring leptin deficiency is of interest and stabilising leptin levels could lead to amelioration of metabolic anomalies (5). Studies have shown that leptin replacement therapy can improve glycemic control and decrease triglyceride and haemoglobin A1C levels, which are markers of lipodystrophy disease severity (14, 115).

A recent multi-society guideline publication establishes that metreleptin therapy is effective for metabolic complications in hypoleptinemic patients with generalised lipodystrophy and selected patients with partial lipodystropy (116). Owing to the rarity of this disease state, no published data provide utility values for use in economic analyses. The present study was undertaken in order to estimate the disutility of the indicated populations of metreleptin.

17.5.1.1 Study Objectives

To evaluate the burden associated with lipodystrophy by measuring the disutility associated with various attributes of lipodystrophy.

17.5.2 Methods

17.5.2.1 Study Design

The study involved the analysis of data generated by a discrete choice experiment (DCE), in which respondents chose between two hypothetical health profiles that differed in levels of impairment and life expectancy (116, 117).

17.5.2.2 Sample Selection and Construction

The study population consisted of the general population from each of the six respective countries (United States and EU5 – United Kingdom, France, Germany, Italy, and Spain). A market research firm, Survey Sampling International (SSI), was retained to recruit 250 respondents in the United States and 150 in each of the EU5 countries, for a total sample of 1,000. In the United States, SSI was instructed to set quotas in order for the final sample to match the US census on gender, age, region (Northeast, Midwest, South, West), and education. In each of the EU5 countries, SSI was instructed to set quotas for the final sample to match Eurostat demographic characteristics for that country.

17.5.2.3 Privacy and Ethics

The participants in this study were only identified by an identity number, and no personal information (name, address, employer, contact information) was collected. Analysis Group and Aegerion only had access to anonymised datasets produced by SSI.

The study was reviewed for legal compliance by Analysis Group and Aegerion.

Required approvals from Independent Review Committee were obtained before the data collection process was initiated.

17.5.2.4 Discrete Choice Experience Survey

SSI recruited respondents in each country through respondent panels. Members of SSI's respondent panels had already agreed to participate in surveys in exchange for compensation. Potential recruits were sent the survey link via email or through the SSI dashboard. Participants who agreed to take the survey clicked through the link in the email.

The survey consisted of three modules: (1) a demographic questionnaire, (2) a tutorial informing respondents of the disease and its associated attributes, and (3) a conjoint survey in which participants were asked to choose their most preferred health profile from two choice cards. Only participants who gave accurate responses to diagnostic questions at the end of the tutorial were allowed to proceed to the conjoint survey. Choice cards represent hypothetical patients and were constructed by assigning values to disease attributes of interest and varying these values across the two cards.

In the second module, respondents viewed a two-part tutorial (summarized on

Table 66, and fully presented in section 17.5.4) and answered a diagnostic question following each part. Those who spent less than four minutes reviewing the first part, or less than two minutes reviewing the second part were automatically excluded from proceeding onto the third module and were not counted towards the respondent quota. Respondents were also excluded from proceeding if they gave incorrect responses to both diagnostic questions and likewise were not counted towards the respondent quota.

Table 66: Topics in Each Part of Survey Tutorial

Part 1	Part 2
▪ Instructions for undertaking the survey ▪ Description of survey pages ▪ Example comparison screen (different for male or female respondents) ▪ List of patient situation attributes ▪ Lipodystrophy – An introduction ▪ Organ damage ▪ Heart damage ▪ Liver damage ▪ Kidney damage ▪ Pancreas damage ▪ Uncontrolled constant hunger (hyperphasia)	▪ Impaired ability to perform work/school work ▪ Impaired physical appearance (different for male or female respondents) ▪ Disruption to female reproductive functioning (female respondents only) ▪ Depression ▪ Chronic pain ▪ Eye damage (retinopathy) ▪ Nerve damage (neuropathy) ▪ Amputation (e.g., toes, limb) ▪ Impaired triglyceride (blood fat) control ▪ Impaired blood sugar control ▪ Risk of developing neutralizing antibodies ▪ Lymphoma risk (a type of blood cancer)

The third module presented respondents with 14 choice tasks. Each task required participants to choose between two choice cards composed of 12 (out of a possible 20) attributes (see Table 67). Attributes appeared in random order across

respondents, but in the same order for each respondent across tasks. Age and life expectancy, however, were always at the top of the choice card, and the position of organ abnormality attributes were randomised as a cluster. This module yielded data describing which of the two choice cards were chosen, along with their attributes.

Table 67: Summary of Attributes and Levels for Discrete Choice Experiment

Features	Levels
Age	5 / 25 / 45
Life expectancy (expected age at death)	If age is 5: 15, 25, 45, 65 If age is 25: 35, 45, 65, 85 If age is 45: 55, 65, 85, 105
Remaining life years	= Life expectancy − age
Heart damage	Present / Absent
Liver damage	Present / Absent
Kidney damage	Present / Absent
Pancreas damage	Present / Absent
Progression of organ damage	No change / Slow / Fast
Ability to perform work / school work	Able / Unable
Uncontrollable constant hunger (hyperphagia)	Present / Absent
Impaired physical appearance	Present / Absent
Disruption to female reproductive functioning (Shown to women only)	No damage / Polycystic ovary syndrome / Infertility
Depression	Present / Absent
Chronic pain	Present / Absent
Eye damage (retinopathy)	Present / Absent
Nerve damage (neuropathy)	Present / Absent
Amputation (eg, toes, limb)	Present / Absent
Triglycerides (blood fat) control	No response or worsening / Partial response / Achieved goal
Impaired blood sugar control	No response or worsening / Partial response / Achieved goal / Achieved goal with hypoglycemia
Risk of loss of response to treatment / Development of neutralizing antibodies	Standard risk / Increased risk due to development of neutralizing antibodies
Lymphoma (a type of blood cancer)	Standard risk / Increased risk

17.5.2.5 Quality Adjusted Life-Year (QALY) Estimation

The conjoint survey data above was used to estimate a multinomial logit model, with a specification that assumed that individuals derive utility from spending time in particular health states. The estimation framework was adopted from the QALY estimation literature (Bansback, et al, 2012; Viney, et al, 2014). Under this

framework, the utility function that respondents were assumed to maximize with their choices was the following:

$$U = T \times \left(\beta_0 + \sum_i \beta_i x_i \right) + \varepsilon,$$

where T was the individual's remaining life, β_0 was the coefficient that quantifies how much utility was derived from a year of perfect health, β_i was the coefficient that quantifies the additional (dis)utility generated by attribute i, x_i was an attribute indicator variable that took a value of 1 whenever attribute i was impaired, and ε was an error term. For the two fertility attributes, the analysis also included an indicator variable (taking a value of 1 for female respondents) that multiplied the product of coefficient and attribute indicator variable.

The utility function above evaluated each choice card that respondents faced. The multinomial logit model estimation assumed that, whenever the utility of choice card A was greater than that of choice card B, it is more likely to be chosen by the respondent. The error term captured the idea that the precise utility value generated by each option is unobserved by the researcher. Choice cards also contained information about the age of the hypothetical patient. This variable allowed conditioning of the QALY weight of attributes by a patient's age, potentially yielding different weights for paediatric patients. In the main estimation model, however, age was omitted, thereby introducing the potential for omitted variable bias. When age was included, some coefficients (and hence QALY weights) differ significantly (in a statistical sense) between patients of different ages. Excluding age implied that the analysis effectively calculated the QALY weights for a hypothetical patient of average age.

Another modelling decision was to exclude an intercept from the regression equation. This was motivated by internal consistency concerns – without an intercept, the utility function could be accurately interpreted as the flow utility obtained from spending *T* years in some health state characterised by an attribute profile, and the utility of death was rendered equal to zero (as per the QALY framework) since a health profile in which a patient dies implies that *T = 0*. The intercept was also excluded in Viney, et al (2014), who report that its impact on the calculated QALY weights was negligible. The same applied to our case, except for the progression of organ abnormality coefficient, the magnitude of which changed by 20% across the two estimation approaches. However, the contribution of this single coefficient to the overall study conclusions was negligible. Overall, the benefits of excluding the intercept in terms of parsimony and consistency outweighed the costs.

Having estimated the coefficients as described above, the analysis generated QALY weights associated with each attribute. These weights described the decrease in utility associated with attribute impairment as a fraction of the utility from spending a year in perfect health. The standard approach in the literature (including the two papers cited above) was to divide the estimated attribute coefficient by the coefficient for the utility from perfect health:

$$QALY\ weight\ of\ attribute\ i = \frac{\beta_i}{\beta_0}$$

The justification for this formula derived from the interpretation of these coefficients as marginal utilities generated by spending a year in some health state (see the derivation on page 735 in Viney, et al [2014]). This process generated estimated QALY weights that captured the extent to which attribute impairment affected individual choices. A negative QALY weight associated with a particular attribute level implies that a respondent was less likely to choose a profile in which the attribute is impaired, with all other factors remaining the same. The larger the QALY weight (in absolute value), the less likely it was that a respondent would choose a profile in which it is impaired. These weights, therefore, captured the relative importance of each attribute for a patient's utility.

17.5.3 Results

A total of 1,000 respondents were surveyed in the United States (n=250), United Kingdom (n=150), France (n=150), Germany (n=150), Italy (n=150), and Spain (n=150). The information generated by these surveys were pooled into a single dataset and estimated a multinomial logit model in which the dependent variable was the choice made by each respondent, and covariates were indicators for whether or not a particular attribute was impaired in a choice card. Coefficients from this multinomial model were rescaled into QALY weights that ranged from −0.27 QALY for amputation to +0.03 for slow progression of organ damage (see **Error! Reference source not found.**) The analysis was replicated for only respondents for the United Kingdom (see Table 70).

Table 68: Per-period Disutility Toll from Lipodystrophy-Related Complications for all samples

Health State	Utility Value	95% Confidence Interval
Heart abnormality	−0.19	−0.20; −0.17
Liver abnormality	−0.15	−0.17; −0.13
Kidney abnormality	−0.13	−0.14; −0.11
Pancreas abnormality	−0.13	−0.14; −0.11
Slow progression of organ abnormality	0.03	0.01; 0.06
Fast progression of organ abnormality	−0.16	−0.18; −0.14
Unable to perform work/school work	−0.25	−0.27; −0.24
Uncontrolled constant hunger (hyperphagia)	−0.11	−0.13; −0.09
Impaired physical appearance	−0.10	−0.12; −0.08
Disruption to female reproductive functioning - Polycystic Ovary Syndrome	−0.06	−0.08; −0.03
Disruption to female reproductive functioning - Infertility	−0.17	−0.20; −0.14
Depression	−0.18	−0.19; −0.16
Chronic Pain	−0.15	−0.17; −0.13
Eye damage (Retinopathy)	−0.19	−0.21; −0.17
Nerve damage (Neuropathy)	−0.16	−0.18; −0.13
Amputation (eg toes, limb)	−0.27	−0.29; −0.25
Triglyceride (blood fat) control – No response or worsening	−0.11	−0.13; −0.09
Triglyceride (blood fat) control – Partial response	−0.05	−0.07; −0.03
Impaired blood sugar control – No response or worsening	−0.18	−0.20; −0.16
Impaired blood sugar control – Partial response	−0.08	−0.10; −0.06
Impaired blood sugar control – Achieved goal with hypoglycemia	−0.06	−0.08; −0.04
Increased risk of loss of response to treatment/development of neutralizing antibodies (eg, with additional medication)	−0.15	−0.17; −0.13
Increased risk of lymphoma (a type of blood cancer)	−0.13	−0.15; −0.11

Table 69: Per-period Disutility Toll from Lipodystrophy-Related Complications for all UK samples

Health State	Utility Value	95% Confidence Interval
Heart abnormality	-0.16	−0.20; −0.13
Liver abnormality	-0.17	−0.23; −0.11
Kidney abnormality	-0.13	−0.17; −0.09
Pancreas abnormality	-0.07	−0.11; −0.02
Slow progression of organ abnormality	-0.01	-0.07; 0.05
Fast progression of organ abnormality	-0.20	−0.24; −0.15
Unable to perform work/school work	-0.23	−0.27; −0.19
Uncontrolled constant hunger (hyperphagia)	-0.12	−0.17; −0.07
Impaired physical appearance	-0.06	−0.11; −0.01
Disruption to female reproductive functioning - Polycystic Ovary Syndrome	-0.05	−0.11; 0.01
Disruption to female reproductive functioning - Infertility	-0.13	−0.20; −0.07
Depression	-0.20	−0.24; −0.16
Chronic Pain	-0.17	−0.22; −0.12
Eye damage (Retinopathy)	-0.22	−0.27; −0.17
Nerve damage (Neuropathy)	-0.10	−0.16; −0.04
Amputation (eg toes, limb)	-0.27	−0.32; −0.22
Triglyceride (blood fat) control – No response or worsening	-0.09	−0.14; −0.03
Triglyceride (blood fat) control – Partial response	-0.02	−0.07; 0.03
Impaired blood sugar control – No response or worsening	-0.21	−0.26; −0.16
Impaired blood sugar control – Partial response	-0.09	−0.15; −0.03
Impaired blood sugar control – Achieved goal with hypoglycemia	-0.09	−0.15; −0.02
Increased risk of loss of response to treatment/development of neutralizing antibodies (eg, with additional medication)	-0.11	−0.16; −0.06
Increased risk of lymphoma (a type of blood cancer)	-0.13	−0.18; −0.08

For the purpose of calculating the utility decrement associated with a particular health attribute, we calculate the ratio of two coefficients. Specifically, the coefficient on the attribute itself (interacted with life expectancy) divided by the coefficient on life expectancy.

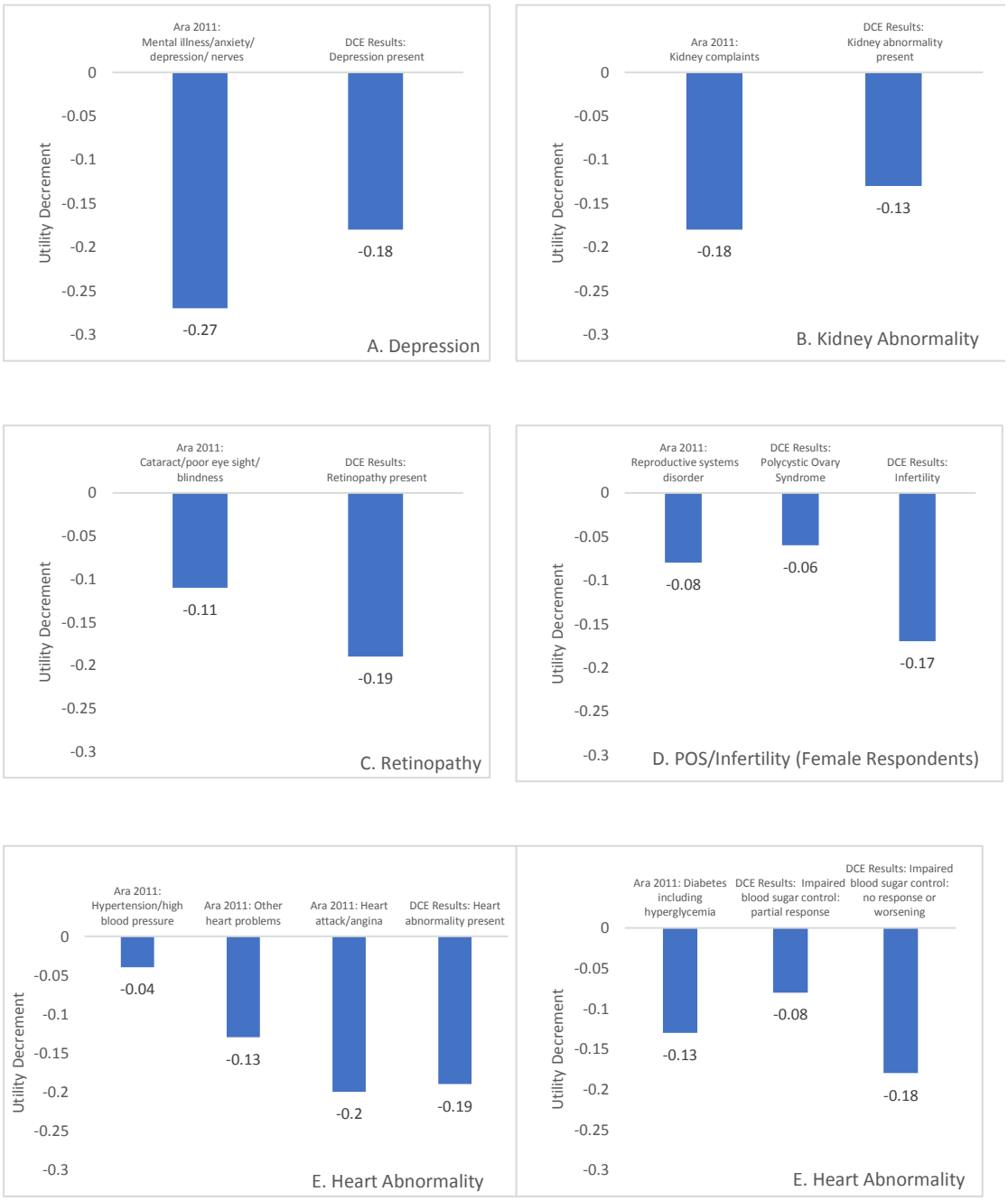
We know that each coefficient individually follows a Normal distribution given the large sample size of 1,000 respondents in our experiment, but the distribution of the ratio of coefficients is unknown.

Here, the bootstrap method of estimation through repeated samples with replacement allows us to calculate a set of coefficient ratios. For each coefficient of interest, we use the point estimate and the variance as parameters to randomly generate a large sample of draws. Once this is done for each coefficients, we can generate a large set of ratios. We can then determine where the 2.5 and 97.5 percentiles of the distribution lie, providing the confidence interval of interest.

To validate the per-period utility decrement estimates Figure 33 compares the estimated values with published literature. (93) The benchmark analysis used here by Ara (2011) used 4 surveys of 41,174 respondents in England to estimate health-state utility values for a wide range of conditions. The purpose of the analysis was to provide utility values for populations in which the condition-specific values were not available. It is a good benchmark for its broad scope in an English population.

The comparison between health-state utility values in the DCE and Ara (2011) generally validated the settings of the new study . The relevant mental health value was slightly higher than “Depression present” in the DCE, but the DCE’s health state only included depression. The value for “Kidney abnormality present” was similar to “Kidney complaints” in Ara (2011). “Retinopathy present” had a greater utility decrement than the broader term in Brazier (2010) (i.e., containing less severe illnesses in addition to retinopathy), “Cataract/poor eye sight/blindness.” Similarly, “Infertility” in DCE was greater than the broader term in Ara (2011), “Reproductive systems disorder”—which was, moreover, similar to the DCE value for “Polycystic ovary syndrome.” Likewise, the DCE health state utility value for “Heart abnormality present” was similar to “Heart attack/angina” in Ara (2011) but was a greater decrement than the less severe “Other heart problems” and “Hypertension/high blood pressure.” Finally, the Ara (2011) health state utility value for “Diabetes” was about midway between the values for the corresponding low- and high-severity “Impaired blood sugar control” health states in the DCE, “partial response” and “no response or worsening.”

Figure 33: Validation of utility decrement estimates vs published literature (93):



17.5.4 Utility Study Tutorial

In what follows, you will be asked to compare alternative patient health situations

Specifically:

1. **You will first review key features of lipodystrophy – a rare and potentially severe illness – or its treatment**
2. **Then, you will be presented with a series of screens, each presenting two separate patient disease situations for you to compare. For each screen, you will be asked to:**
   a. **Review how the features differ between the two situations;**
   b. **Choose which of the two situations you would prefer to live with.**

Your choices are very important, and will help guide the development of new treatments for lipodystrophy

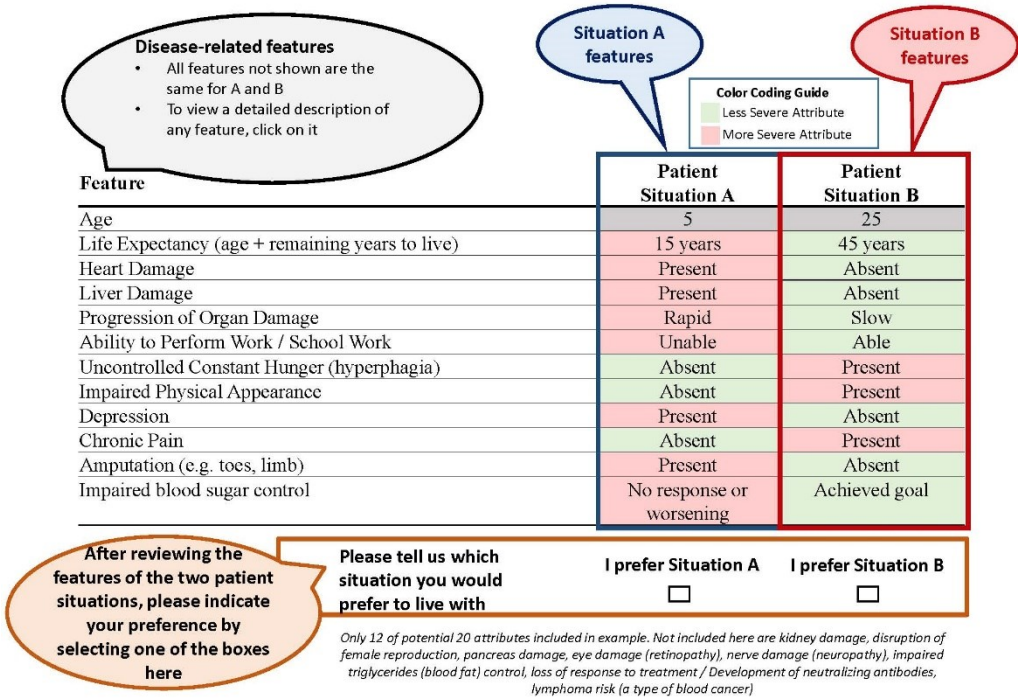
What you will see

1. **On the next screen, we will show you an example of such a "comparison screen" with two patient disease situations described**
   - Comparison screens will provide information on key features of the disease (up to 12 at a time)
   - To the extent that some features of the disease are not shown on the screen, please assume that they do not differ between the two patient situations

2. **After that, we will show you a full list of all the potential 20 [19 for men] key features of lipodystrophy**

3. **Finally, before we start asking you to compare patient situations, we'll provide ~~with~~ you with some important background information on each potential feature of the disease, so that you are able to compare patient situations with these features**

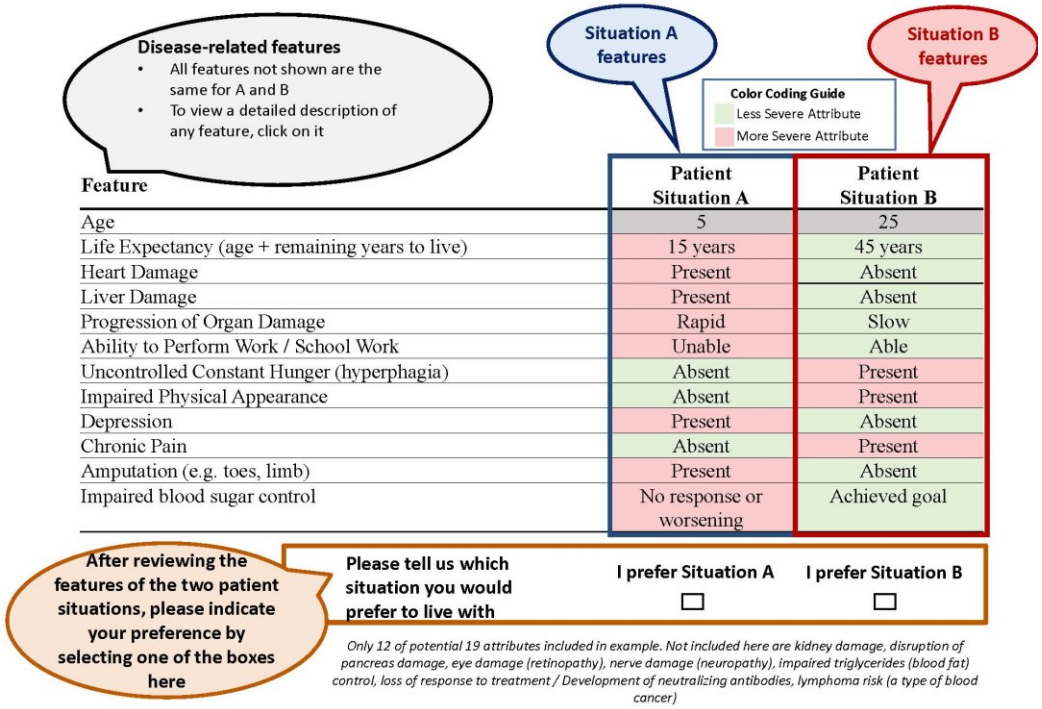
Example of a Comparison Screen Summarizing Features of Two Situations (A and B)



Feature	Patient Situation A	Patient Situation B
Age	5	25
Life Expectancy (age + remaining years to live)	15 years	45 years
Heart Damage	Present	Absent
Liver Damage	Present	Absent
Progression of Organ Damage	Rapid	Slow
Ability to Perform Work / School Work	Unable	Able
Uncontrolled Constant Hunger (hyperphagia)	Absent	Present
Impaired Physical Appearance	Absent	Present
Depression	Present	Absent
Chronic Pain	Absent	Present
Amputation (e.g. toes, limb)	Present	Absent
Impaired blood sugar control	No response or worsening	Achieved goal

Only 12 of potential 20 attributes included in example. Not included here are kidney damage, disruption of female reproduction, pancreas damage, eye damage (retinopathy), nerve damage (neuropathy), impaired triglycerides (blood fat) control, loss of response to treatment / Development of neutralizing antibodies, lymphoma risk (a type of blood cancer)

Example of a Comparison Screen Summarizing Features of Two Situations (A and B)



Feature	Patient Situation A	Patient Situation B
Age	5	25
Life Expectancy (age + remaining years to live)	15 years	45 years
Heart Damage	Present	Absent
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Progression of Organ Damage	Rapid	Slow
Ability to Perform Work / School Work	Unable	Able
Uncontrolled Constant Hunger (hyperphagia)	Absent	Present
Impaired Physical Appearance	Absent	Present
Depression	Present	Absent
Chronic Pain	Absent	Present
Amputation (e.g. toes, limb)	Present	Absent
Impaired blood sugar control	No response or worsening	Achieved goal

Only 12 of potential 19 attributes included in example. Not included here are kidney damage, disruption of pancreas damage, eye damage (retinopathy), nerve damage (neuropathy), impaired triglycerides (blood fat) control, loss of response to treatment / Development of neutralizing antibodies, lymphoma risk (a type of blood cancer)

Patient situation attributes you will be asked to consider include:

- Age
- Life expectancy (expected age at death)
- Organ damage and its speed of progression
  - Heart Damage
  - Liver Damage
  - Kidney Damage
  - Pancreas Damage
- Ability to perform work / school work
- Uncontrolled constant hunger (hyperphagia)
- Impaired physical appearance
- Disruption to female reproductive functioning [Show to women only]
- Depression
- Chronic Pain
- Eye damage (retinopathy)
- Nerve damage (neuropathy)
- Amputation (e.g. toes, limb)
- Triglycerides (blood fat) Control
- Impaired blood sugar control
- Risk of Loss of Response to Treatment / Development of Neutralizing Antibodies
- Lymphoma risk (a type of blood cancer)

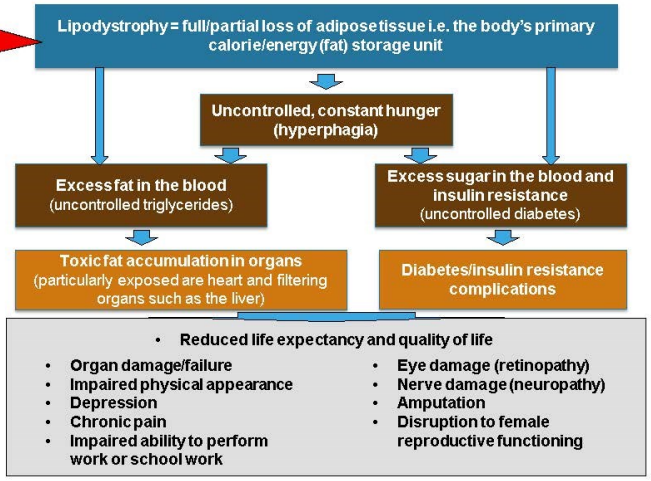
In the following slides, we provide with you with some important background information on the disease and its features, so that you are able to compare patient situations with these features

Lipodystrophy – An introduction

Lipodystrophy – An introduction

Extremely rare disease with very few, mostly pediatric patients. No cure and very limited treatment options

- **In healthy people, adipose cells store ~95% of the body's energy**
- **Only about 1 person in a million** has lipodystrophy (or ~300 patients in the US)
- Most patients suffering from generalized lipodystrophy are diagnosed as **children, and may have experienced symptoms as early as in the womb**



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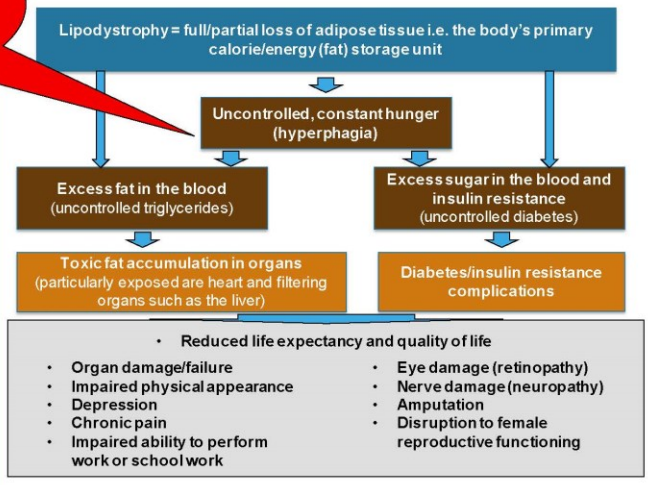
Lipodystrophy – An introduction (cont.)

Hyperphagia (uncontrolled, constant hunger) can be debilitating and has a potentially critical role in driving fat/sugar intake and progression/ impact of disease

"her hunger rages were violent and lasted all day."
mother of a lipodystrophy patient

***"Appetite was a major issue from birth**...It's gotten so bad that [she] has pulled her hair out for food. She has scratched her face and ran into walls head first. **She fights anything and anyone in her path and screams until she gets what she wants which is always always, always food**. She took no hesitation with sticking whatever she could in her mouth to attempt to soothe her starvation."*
mother of a lipodystrophy patient

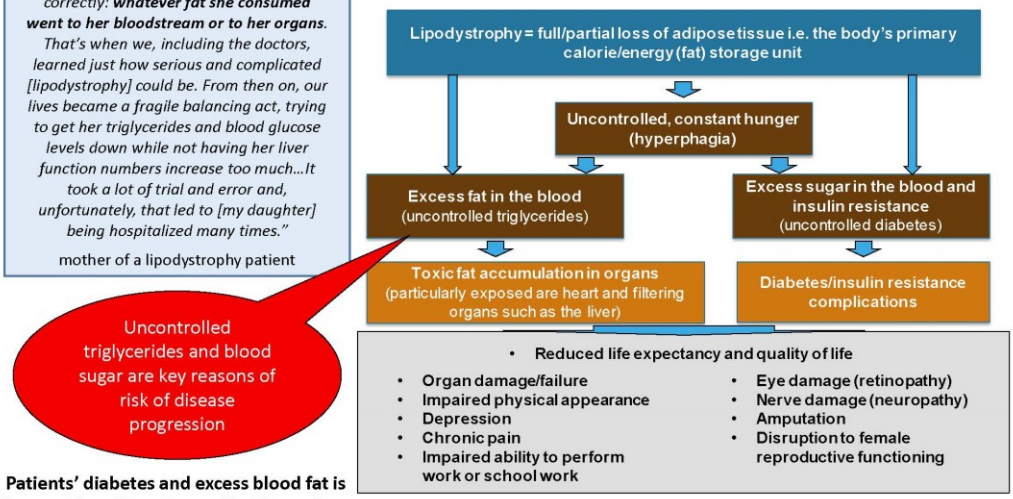
*"Because of [lipodystrophy], **she was incredibly hungry all the time and she was obsessed with food!** All of her clothes had food on them and even her favorite toys were food! So, we made a rule that she could only eat once an hour and she lived by the clock. As soon as it was a new hour, she was asking for a snack!"*
mother of a lipodystrophy patient



Lipodystrophy – An introduction (cont.)

*"We discovered her body didn't process fat correctly: **whatever fat she consumed went to her bloodstream or to her organs**. That's when we, including the doctors, learned just how serious and complicated [lipodystrophy] could be. From then on, our lives became a fragile balancing act, trying to get her triglycerides and blood glucose levels down while not having her liver function numbers increase too much…It took a lot of trial and error and, unfortunately, that led to [my daughter] being hospitalized many times."*

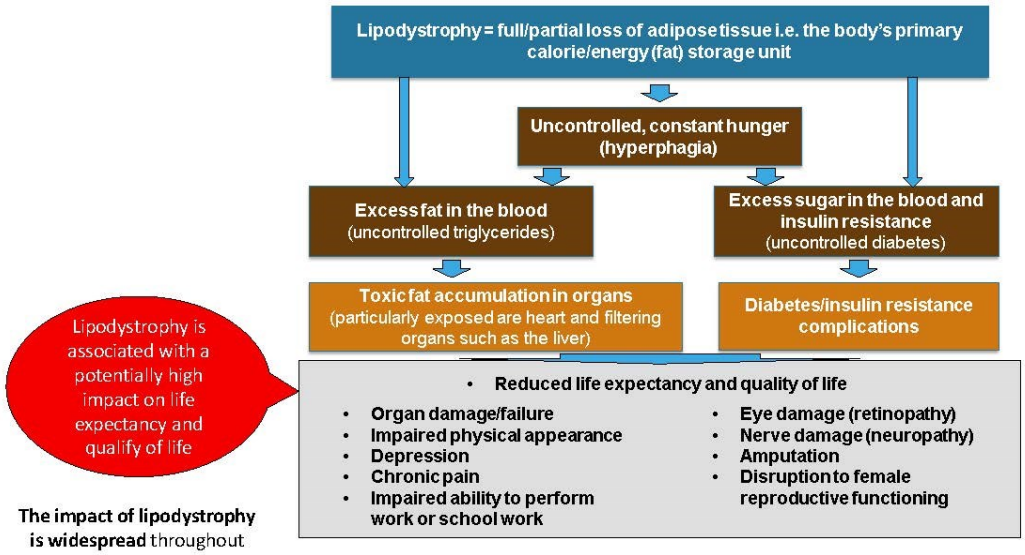
mother of a lipodystrophy patient



Uncontrolled triglycerides and blood sugar are key reasons of risk of disease progression

Patients' diabetes and excess blood fat is frequently resistant to medication (e.g. even with very high doses of insulin patients' diabetes may not be controlled)

Lipodystrophy – An introduction (cont.)



Lipodystrophy is associated with a potentially high impact on life expectancy and qualify of life

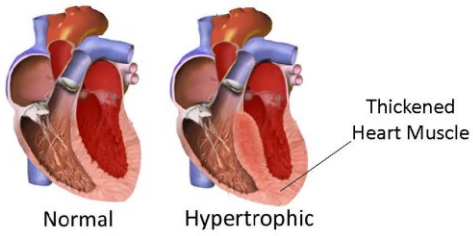
The impact of lipodystrophy is widespread throughout the body

Organ Damage

- **In lipodystrophy patients, the ability to store fat is impaired, leading to excessive fat in the blood**
- **Fat deposits can occur in a number of organs, resulting in significant damage to the following organs:**
  - Heart
  - Kidney
  - Liver
  - Pancreas
- **Progression of organ damage can be:**
  - **No change** e.g. no new organ damage occurring
  - **Slow** e.g. a new organ is damaged within 10+ years
  - **Fast** e.g. a new organ is damaged within the next 3 years or so
- **Potential consequences of organ damage may include:**
  - Significant health complications
  - Need for organ transplantation
  - Early death

Heart Damage

- **Heart damage associated with lipodystrophy can include:**
  - **Cardiomyopathy** – Disease where the heart weakens by becoming enlarged, thick, or rigid
  - **Heart failure** – When the heart cannot pump blood well due to diseases that damage the heart
  - **Myocardial infarction (heart attack)** – Permanent heart muscle cell damage from completely blocked arteries
  - **Arrhythmia** – heart beats at irregular rhythm
- **Potential consequences may include:**
  - Need to take regular medications
  - Chest pain (angina)
  - Impaired quality of life
  - Need for surgery
  - Early death



Liver Damage

- **The liver's main job is to filter the blood coming from the digestive tract, before passing it to the rest of the body.**
- **In lipodystrophy patients, the ability to store fat is impaired and fat deposits occur in the liver, resulting in significant organ damage**
- **Liver damage associated with lipodystrophy can include:**
  - **Hepatomegaly** - Enlarged liver
  - **Hepatic steatosis** - fatty liver disease
  - **Steatohepatitis** - fatty liver disease with simultaneous fat accumulation in the liver
  - **Cirrhosis** – scarring of the liver
  - **Liver failure** – loss of liver function
- **Potential consequences of liver damage may include:**
  - Loss of weight and appetite
  - Extreme fatigue, weakness
  - Hallucinations, confusion or trouble concentrating
  - Vomiting of blood
  - Early death

Example of 2 sibling patients with enlarged abdomen due to hepatomegaly

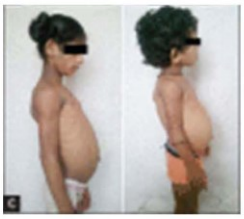
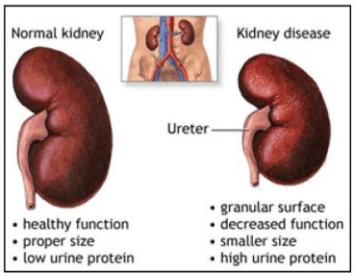


Image Reference:
http://www.idoj.in/article.asp?issn=2229-5178;year=2014;volume=5;issue=5;spage=20;epage=22;aulast=Rao

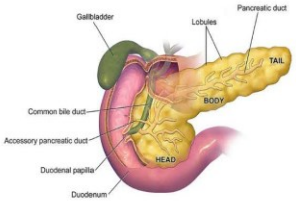
Kidney Damage

- **The kidney's main job is to further filter blood from the liver and produce urine to remove waste**
- **Kidney damage associated with lipodystrophy can include:**
  - **Chronic kidney disease** - Gradual loss of kidney function over time
  - **Nephropathy** - Kidney damage, typically caused by diabetes
  - **Kidney failure** – Full loss of kidneys' ability to remove waste and balance fluids
- **Potential consequences of kidney damage may include:**
  - Need to be put on dialysis
  - Need for kidney transplantation
  - Early death



Pancreas Damage

- **The pancreas plays an essential role in converting the food we eat into fuel for the body's cells. It has two main functions:**
  - Helping digestion via the release of digestive enzymes
  - Regulating blood sugar via the release of insulin and glucagon
- **In lipodystrophy patients, the ability to store fat is impaired and fat deposits occur in the pancreas, resulting in significant organ damage**
  - Excessive blood sugar levels may also result in pancreatic damage
- **Pancreas damage associated with lipodystrophy can include:**
  - **Pancreatitis** – inflammation of the pancreas typically happening when the digestive enzymes are activated before they are released into the small intestine and begin attacking the pancreas
  - **Diabetes**
- **Potential consequences of pancreas damage may include:**
  - Need to medicate patient to address diabetes, pancreatitis (pancreas inflammation) and their complications
  - Abdominal pain
  - Severe pancreatitis can also harm other vital organs such as the heart, lungs, and kidneys
  - Early death



Uncontrolled Constant Hunger (Hyperphagia)

- **Lipodystrophy patients typically suffer from uncontrolled, constant hunger**
  - Patients may be obsessed with food intake (e.g. parents may have to put locks on fridges and/or food cupboards)
- **This can result in significant excess fat and sugar intake**
  - Some patients report eating significantly more than other family members and still not achieve satiety
- **With nowhere to be stored** (lacking or impaired fat cells)**, the excess fat may be deposited in organs** (e.g. liver, heart, pancreas, kidney) **creating significant damage to these organs**
- **In addition, excess fat and sugar in the blood can result in:**
  - High triglycerides (blood fat)
  - Diabetes (high blood sugar levels)
- **Thus potential consequences of hyperphagia may include:**
  - Impaired social functioning (incl. ability to work/go to school)
  - Depression and other mental health complications (e.g. anxiety)
  - Long-term diabetes complications (e.g. amputation, nerve damage [neuropathy], [retinopathy], etc.)
  - Faster organ damage progression
  - Early death

Because of [lipodystrophy], she was incredibly hungry all the time and she was obsessed with food! All of her clothes had food on them and even her favorite toys were food! So, we made a rule that she could only eat once an hour and she lived by the clock. As soon as it was a new hour, she was asking for a snack!

mother of a lipodystrophy patient

[My daughter] is unable to attend public schooling… Her inability to sit and/or stand for long periods of time along with her excessive appetite and needs to eat every hour or so would cause a disruption to class

mother of a Lipodystrophy patient

Impaired Ability to Perform Work / School Work

- **Lipodystrophy can limit the ability of patients to perform work / school work due to:**
  - Depression / Other mental health issues
  - Hyperphagia
  - Fatigue

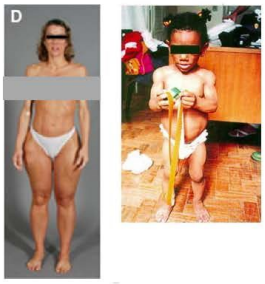
- **Potential consequences may include:**
  - Reduced school / work attendance
  - Impaired school / work performance
  - Low wages / poor work prospects
  - Need to take unpaid leave

Impaired Physical Appearance [Version for women]

- **Lipodystrophy can be associated with severe impairment in physical appearance including the following:**

Skeletal facial features

Extreme muscularity of arms and legs



Excessive facial hair (hirsutism)

Acanthosis nigricans (dark patches of skin with a thick, velvety texture)

- **Potential consequences may include:**
  - Low self esteem
  - Depression
  - Need for esthetic/restorative surgery

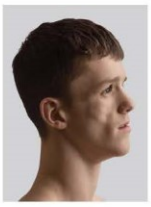
References:

http://www.xdiagnosis.net/causes/lipodystrophy
http://lifeexamples.blogspot.ca/2013/07/lizzie-velasquez.html
http://www.sciencedirect.com/science/article/pii/S0889852916300706
http://www.scielo.br/scielo.php?pid=S0021-75572004000500015&script=sci_arttext&tlng=en
http://www.womens-health-advice.com/photos/hirsutism.html
http://www.healthline.com/health/acanthosis-nigricans#prevention7

Impaired Physical Appearance [Version for men]

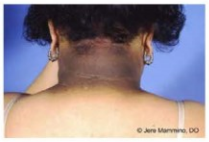
- **Lipodystrophy can be associated with severe impairment in physical appearance including the following:**

Skeletal facial features



Extreme muscularity of arms and legs

Acanthosis nigricans (dark patches of skin with a thick, velvety texture)



- **Potential consequences may include:**
  - Low self esteem
  - Depression
  - Need for esthetic/restorative surgery

References (from left to right):

http://www.xdiagnosis.net/causes/lipodystrophy
http://www.myaleptpro.com/generalized-lipodystrophy

http://www.sciencedirect.com/science/article/pii/S0889852916300706
http://www.scielo.br/scielo.php?pid=S0021-75572004000500015&script=sci_arttext&tlng=en

http://www.healthline.com/health/acanthosis-nigricans#prevention7

[Show to women only]

Disruption to Female Reproductive Functioning

- **Lipodystrophy can be associated with severe disruption to female reproductive functioning including:**
  - **PCOS** (Polycystic ovary syndrome)
    - Situation where a woman's ovaries or adrenal glands produce more male hormones than normal
    - Most women with PCOS grow many small cysts (fluid-filled sacs) on their ovaries
    - PCOS can cause missed or irregular menstrual periods, leading in some cases to infertility; In the general population, PCOS is one of the most common causes of female infertility
    - Other PCOS features can include physical signs such as acne, male-pattern baldness, weight gain, or skin tags (small excess flaps of skin in the armpits or neck area)
  - **Infertility** (i.e. ability for women to have children)

Depression

- **Lipodystrophy can be associated with depression potentially due to a number of factors including:**
  - Impaired physical appearance
  - Hyperphagia (uncontrolled constant hunger)
  - Chronic pain
  - Impaired life expectancy
  - Other quality of life impairment

- **Female patients may be particularly at high risk of depression**

Chronic Pain

- **Lipodystrophy can be associated with chronic pain:**
  - i.e. pain that recurs frequently over time
  - Abdominal pain appears to occur frequently

- **Potential consequences of chronic pain may include:**
  - Continual discomfort
  - Depression
  - Increased stress
  - Fatigue
  - Trouble sleeping
  - Weakness/Lack of energy
  - Need for medication for temporary alleviation of symptoms

"Then came the scary day when [she] complained of pain in her stomach that would not go away. Her stomach became huge, and when we went to hospital, her triglyceride levels were about 2,000. The normal level is around 100. She had pancreatitis, and it was a scary night for all of us."

Mother of a lipodystrophy patient

Eye Damage (Retinopathy)

- **Lipodystrophy can be associated with eye damage known as retinopathy**
  - Retinopathy is a disease of the retina that results in impairment or loss of vision
  - Retinopathy is typically a complication of uncontrolled diabetes

- **Potential consequences of retinopathy may include:**
  - Partial (e.g. blurry vision) or complete vision impairment (blindness)
  - Significantly impaired quality of life

Nerve Damage (neuropathy)

- **Lipodystrophy can be associated with nerve damage (neuropathy):**
  - Nerve damage associated with lipodystrophy is most often in the hands and feet (peripheral)
  - Neuropathy is typically a complication of uncontrolled diabetes

- **Potential consequences of neuropathy may include:**
  - Abnormal sensation in feet and hands
  - Pain which may not be easy to manage with common analgesics (e.g. ibuprofen, opioids, etc.)
  - Impaired muscle movement (in rare cases)

Amputation (e.g. toes, limb)

- **Lipodystrophy can lead to amputation (surgical removal) of extremities or a limb:**
  - Amputation is typically a complication of uncontrolled diabetes, infection, and/or neuropathy
  - Feet extremity (toe) amputations are most common

- **Potential consequences of amputations may include:**
  - Impaired mobility
  - Grief over lost limb / depression
  - Reduced quality of life

Impaired Triglyceride (blood fat) Control

- **Lipodystrophy is typically associated with significantly impaired triglyceride (blood fat) control**
  - Specifically, lipodystrophy frequently leads to excessive levels of triglycerides (fat) in the blood (hypertriglyceridemia)
  - Triglycerides are the main constituents of body fat in humans

- **Potential consequences of impaired triglyceride control may include:**
  - Need to medicate patient to address hypertriglyceridemia and its complications
  - Lipodystrophy complications progression (e.g. organ damage)
  - Increased risk of stroke, heart disease, heart attack
  - Early death

Impaired Blood Sugar Control

- **Lipodystrophy is often associated with significantly impaired blood sugar/glucose control**
  - Specifically, lipodystrophy frequently leads to excessive levels of sugar/glucose in the blood (diabetes)
  - Lipodystrophy is often associated with insulin resistance, and patients may not be able to use medications to achieve blood sugar control, even with very high doses of insulin

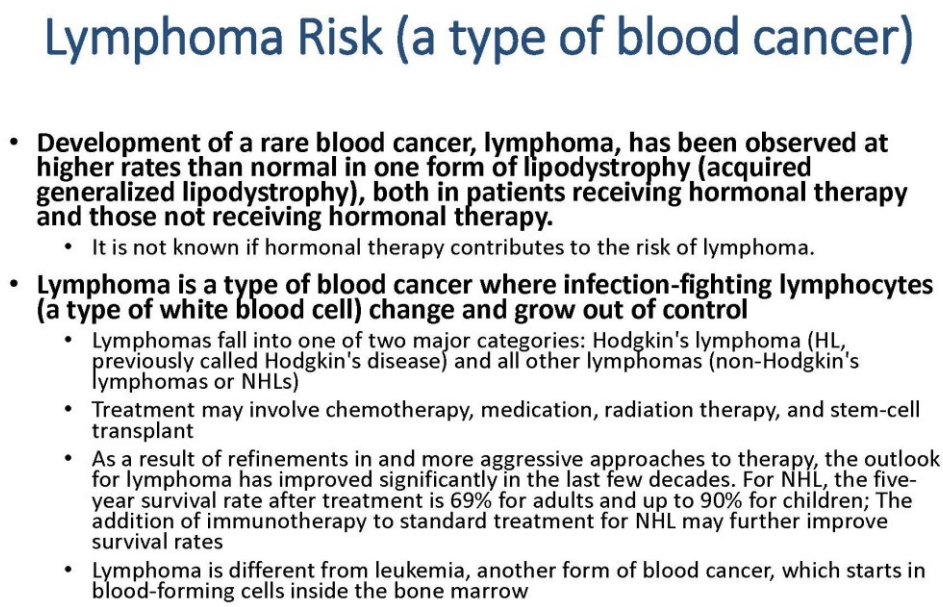
- **Potential consequences of impaired blood sugar control may include:**
  - Patient needs to take medication to address diabetes and its complications
  - Diabetes complications such as nerve damage, amputation (e.g. toes, limb), cardiovascular disease, etc.
  - Increased risk of cardiovascular disease
  - Lipodystrophy complications progression (e.g. organ damage)
  - Early death

Risk of Developing Neutralizing Antibodies

- **Hormonal therapy can help alleviate some of the symptoms of lipodystrophy** (e.g. hyperphagia, triglyceride and blood sugar control, physical appearance, etc.)

- **It has been hypothesized that neutralizing antibodies may reduce response to treatment or worsen the symptoms of lipodystrophy**
  - Neutralizing antibodies may lead to a reduction in natural hormone production by the body

- **Thus far, there are no data which implicate hormonal therapy with a lower treatment response. Although, hormonal therapy might be associated with severe infections.**



17.6 Appendix 6: Survival Study

17.6.1 Background

Lipodystrophy is a rare condition associated with partially or fully absent subcutaneous adipose tissue (body fat under the skin). As a result, fat accumulates in nonadipose tissues, which leads to cosmetic irregularities and, more importantly, to metabolic abnormalities such as insulin resistance, diabetes, and hypertriglyceridemia. These abnormalities often lead to complications and comorbidities such as diabetes mellitus, acute pancreatitis, hepatic steatosis, cirrhosis, cardiovascular disease, diabetic-associated end stage renal disease, and other complications of diabetes ((21, 103, 114, 118)

Due to lack of adipocytes, a marked reduction in leptin levels is often observed in patients with lipodystrophy (3). Leptin is a hormone produced by adipose tissue that regulates several metabolic processes including glucose homeostasis, insulin sensitivity, and fatty acid oxidation (12). Leptin deficiency observed in lipodystrophy leads to the development of numerous metabolic abnormalities. Therefore, restoring leptin deficiency is of interest and stabilizing leptin levels could lead to amelioration of metabolic anomalies (5). Studies have shown that leptin replacement therapy can improve glycemic control and decrease triglyceride and hemoglobin AI1C levels, which are markers of lipodystrophy disease severity (43).

A recent multi-society guideline publication establishes that metreleptin therapy is effective for metabolic complications in hypoleptinemic patients with generalized

lipodystrophy and selected patients with partial lipodystropy (2). While studies have shown that early mortality is associated with generalized lipodystrophy, the effect of metreleptin therapy on mortality has not yet been established.

17.6.1.1 Study objectives

- To estimate and extrapolate the progression of organ abnormalities among patients with lipodystrophy over time, with and without metreleptin treatment;
- To relate organ abnormality progression to mortality;
- To relate metreleptin treatment to mortality directly;
- To simulate survival differences due to metreleptin by combining extrapolated differences in organ abnormality progression with the relationship between organ damage progression and mortality

17.6.2 Methods and Results

17.6.2.1 Estimating and extrapolating progression of organ abnormalities

Abnormalities to four organs are considered: heart, kidney, liver and pancreas. Patient organs are characterised as either having an abnormality or not over the course of a particular year. The following table lists the conditions that result in a patient being categorised as having developed an organ abnormality:

Figure 34: Organ abnormalities

Organ	Condition(s)
Liver	Ectopic fat deposit on liver Hepatomegaly Hepatic steatosis Steatohepatitis Cirrhosis Liver failure
Heart	Cardiomyopathy Heart failure Myocardial infarction Arrhythmia
Kidney	Chronic kidney disease Nephropathy Kidney failure
Pancreas	Pancreatitis

Due to data limitations, the total number of organs with abnormalities that a patient has are tracked but the identity of the afflicted organ is not considered. The number of abnormal organs, which plays a crucial role in the analysis, ranges between 0 and a maximum of 4.

Definition of progression

Progression is defined as an increase in the number of organs with abnormalities that a particular patient has. For example, a patient with a heart abnormality is considered to have progressed in organ abnormality if in the next year, they have also developed an abnormality in their kidney.

Observed progression data

The probability of progression for a patient captures their likelihood of developing abnormalities to an additional organ in the next period. Quantities for progressing from 0 to 1, 1 to 2, 2 to 3, and 3 to 4 organ abnormalities are estimated using data from the generalised and partial lipodystrophy (GL/PL) natural history study and the NIH follow-up study (see section 4.1). Below shows the Kaplan-Meier curves associated with these progression events. All patients begin with the same number of abnormalities; the Kaplan-Meier (KM) curve at each point displays the proportion of patients who have not yet progressed. A horizontal segment in the KM results from a period in which no patients develop additional abnormalities, while a steep segment results from a period in which many patients progressed.

Figure 35: Natural History Study Organ Abnormality Progression

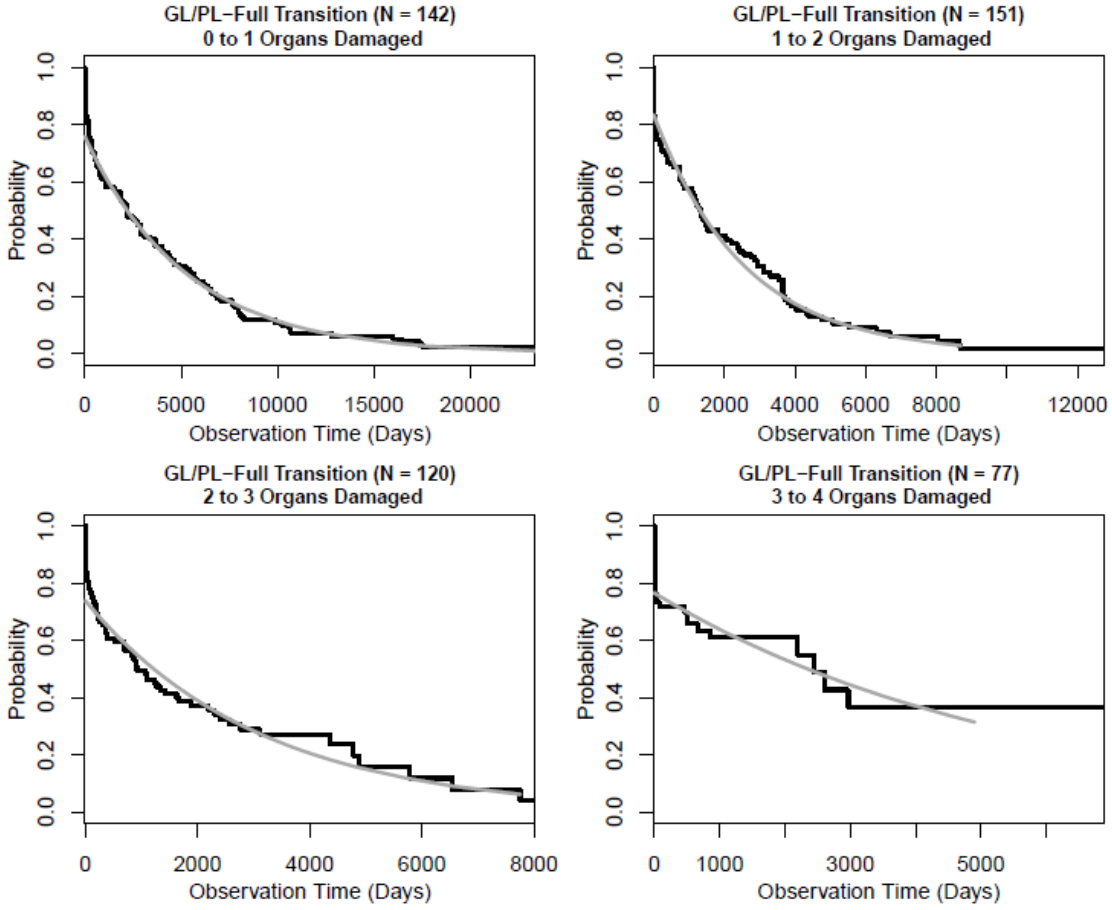
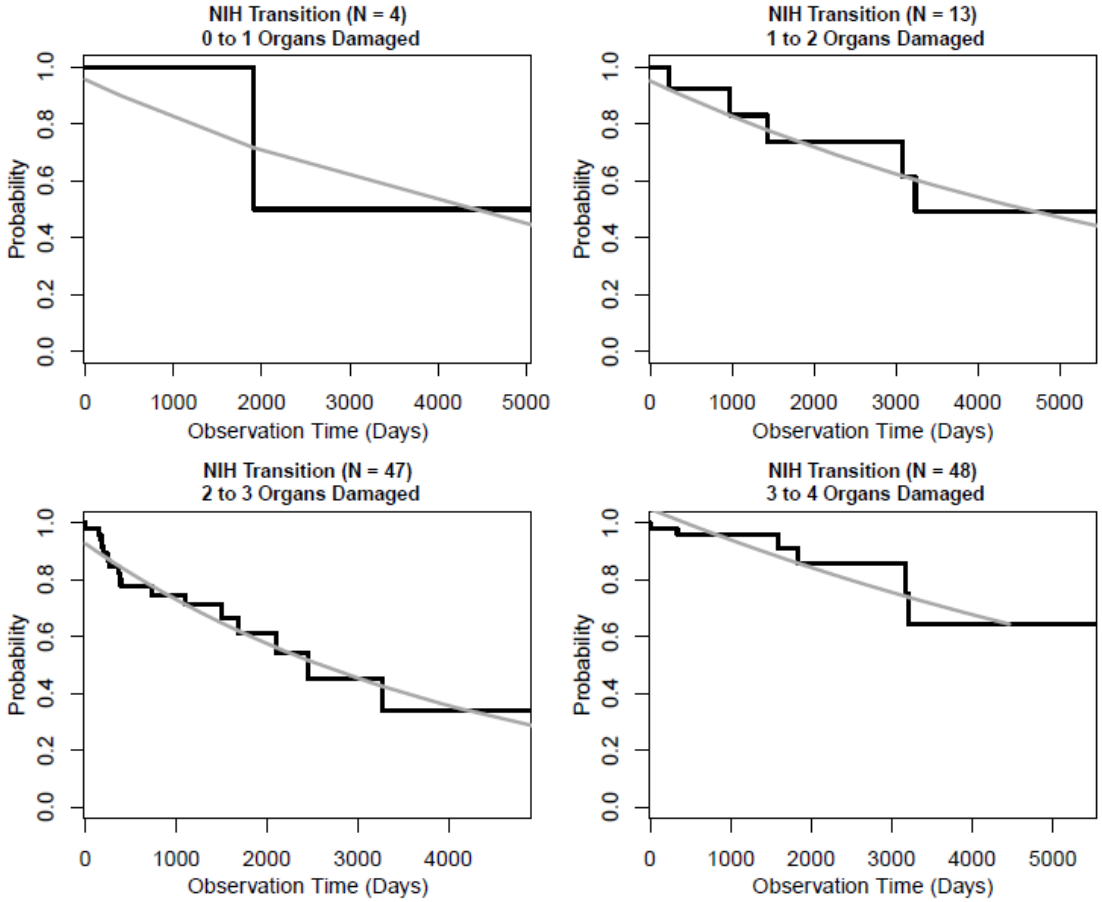


Figure 36: NIH Study Organ Abnormality Progression



Determining transition probabilities and resulting Markov process

It is assumed that organ abnormality events occur continuously and independently across patients and hence are well modelled by an exponential distribution. As such, exponential curves to all the Kaplan-Meier curves above to estimate the associated exponential parameter. The exponential parameter is then log transformed into a per period transition probability. The resulting estimates are summarised in Table 70.

Table 70: Estimated progression probabilities from the natural history study (N=178)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	6.7%	142	127
1 to 2	13.3%	151	112
2 to 3	11.0%	120	76
3 to 4	6.4%	77	30

Estimating transition rates from the NIH Follow-Up study, for patients treated with metreleptin, follows the same approach. However, patients are only observed from their date of treatment (rather than from birth), truncating the data and potentially biasing estimates. The approach described above to generate transition probabilities derived from data on treated patients for the natural history study data is repeated for the NIH data. The results of this exercise are summarised in Table 71.

Table 71: Estimated progression probabilities from the NIH Follow-Up data (N=112*)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	5.4%	4	1
1 to 2	5.0%	13	5
2 to 3	8.3%	47	17
3 to 4	3.9%	48	7

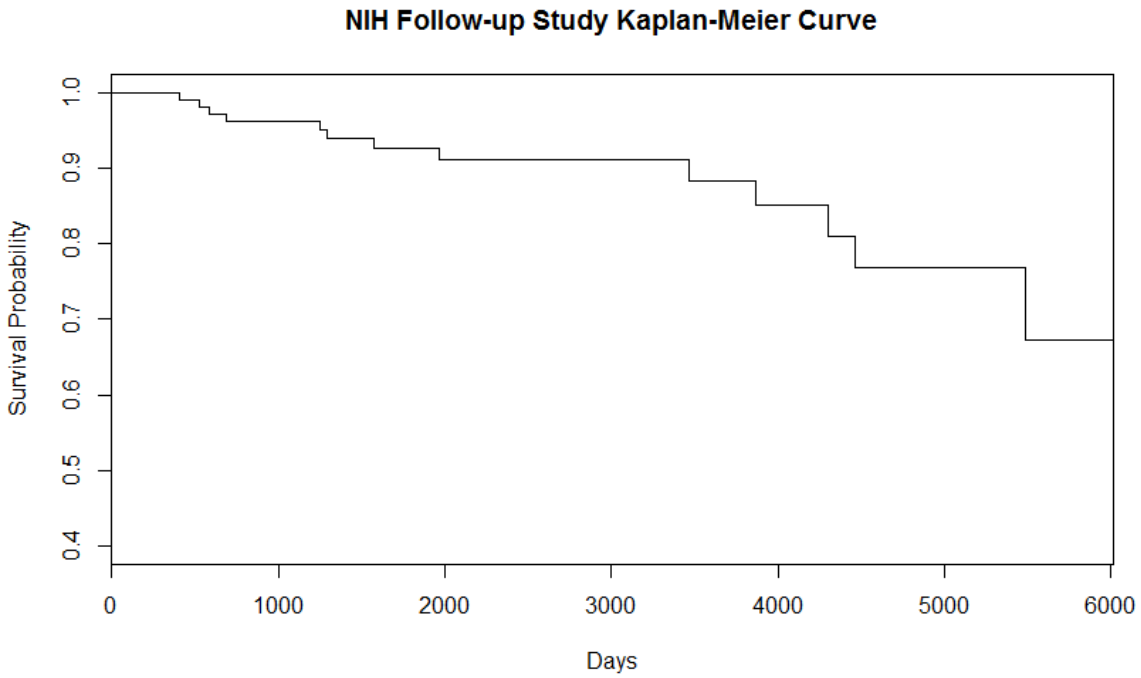
**NIH follow-up study included 114 patients, but sufficient data in the period after baseline is available for only 112*

17.6.2.2 Estimating and extrapolating mortality in NIH study

Observed Mortality

The main survival data derives from the NIH Follow-Up study – a study of 114 patients observed over a maximum of 16.5 years. Below is the Kaplan-Meier curve derived for the entire sample (Figure 37).

Figure 37: Kaplan-Meier curve for entire NIH Follow-Up Study sample



Extrapolation of baseline GL survival using NIH Follow-Up Study

Data from the NIH trial ends after a maximum of 15 years of follow-up. The economic model simulates patient outcomes up to 60 years after the start of treatment. To provide mortality inputs for GL patients in the model, survival curves derived above are extrapolated beyond the end of available data. The approach described in Latimer (2013) and Williams et al. (2017) is followed; fitting a number of parametric models (exponential, Weibull, log-normal, and log-logistic) to the real world data. The best fitting model to the data, as per the AIC test, as well as a visual inspection, is then chosen which concludes that the exponential model is the most appropriate (Table 72). The baseline GL Kaplan-Meier survival curve derived from the NIH data, as well as the fitted parametric survival curves for the modelled time horizon, are shown in Figure 38. The final baseline GL survival curve in the model uses observed survival probabilities for year 0 to 16 and extrapolated exponential survival probabilities for year 17 to 60.

Figure 38: KM vs. fitted parametric baseline GL survival curves

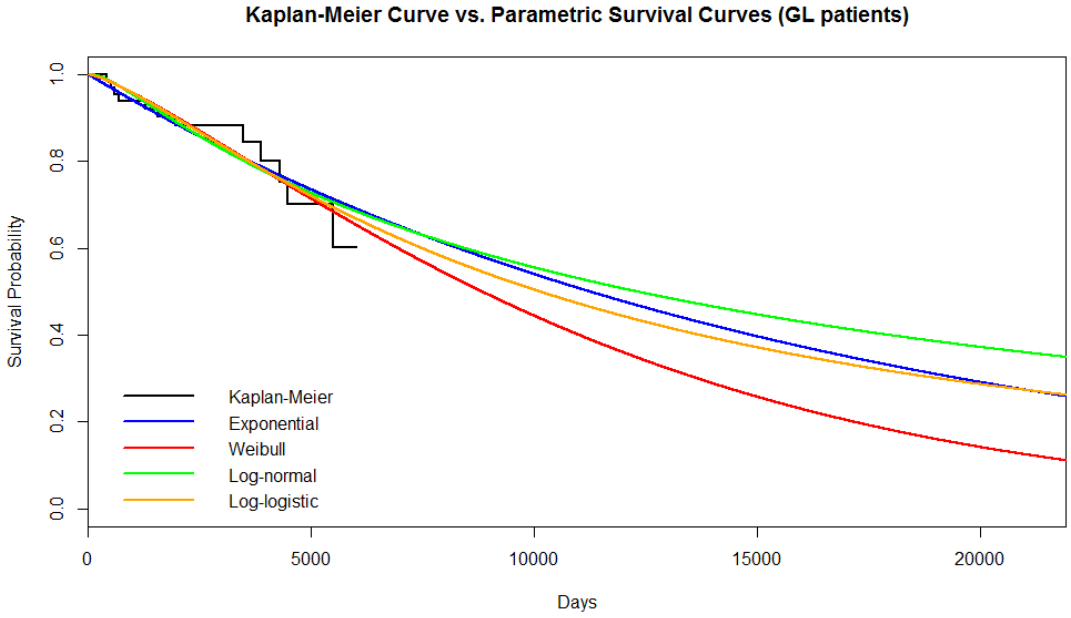


Table 72: Results of AIC test

	df	AIC
Exponential model	1	258.6514
Weibull model	2	259.8144
Log-normal model	2	260.1124
Log-logistic model	2	260.091

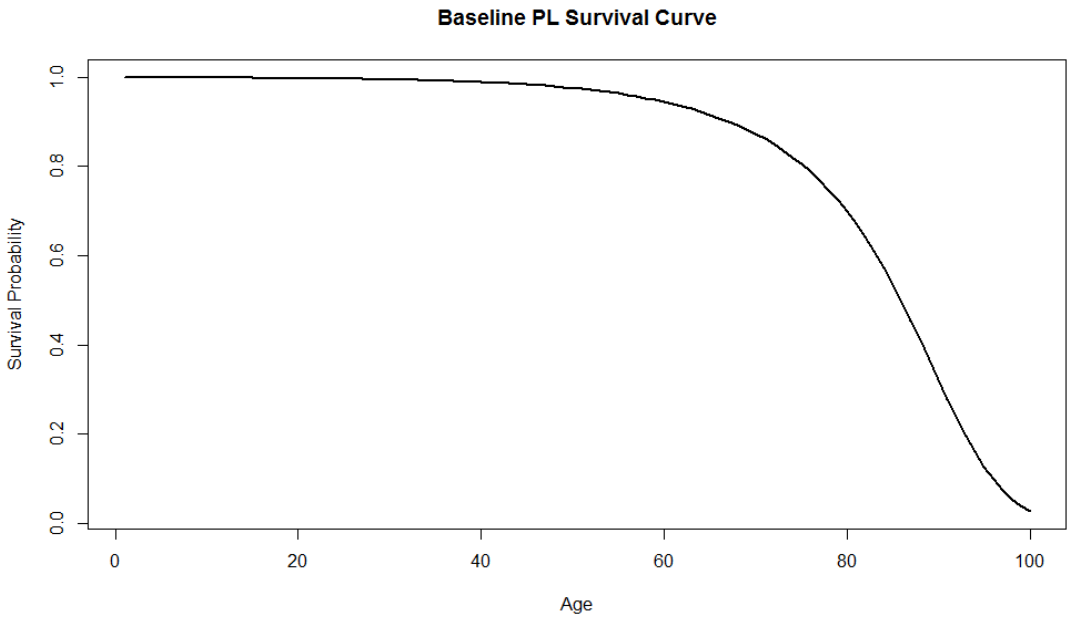
Extrapolation of baseline PL survival using life tables

As PL patients generally experience symptoms and outcomes that are milder than those of GL patients, mortality is modelled separately from GL patients. However, because the number of mortality events among PL patients in the NIH trial is extremely low[3], PL patients' survival were not extrapolated using the NIH Follow-up Study patient-level data. Instead, external data were used to derive the PL baseline survival curve based on an approach summarised by Latimer (2013). To provide mortality inputs for PL patients in the model beyond the 15 years of follow-up time of the NIH Follow-up Study, survival curves are extrapolated using the latest 2014-2016 United Kingdom (UK) national life tables. From the UK life tables, conditional yearly survival probabilities were calculated for the male and female population separately based on the number of survivors in each year for each age group. The gender-specific survival probabilities were subsequently weighted by the proportion of males or females among PL patients in the NIH Follow-Up study to calculate average yearly

[3] Only 1 patient dies during the NIH trial's follow-up period.

survival probabilities and generate the baseline PL survival curve. The final baseline PL survival curve is shown in Figure 39

Figure 39: Baseline PL survival curve based on UK national life tables



17.6.2.3 Relationship between organ abnormality progression and mortality

GL patients have significant organ damage progression and premature mortality. Organ failure is often a common cause of death. The disease course of GL and PL leads to severe morbidity for patients, with multi-organ involvement from an early age. Metabolic abnormalities lead to a host of co-morbidities, many of which are life-threatening. The severe metabolic abnormalities associated with GL occur at a young age and may result in premature diabetic nephropathy, retinopathy, cardiomyopathy, recurrent attacks of acute pancreatitis, hepatomegaly, and organ failure.

Akinci et al. (119), described the natural history of patients with CGL based on the Turkish Lipodystrophy Study Group. The study highlighted the early onset of severe metabolic complications in these patients. As a consequence, these patients also develop end-organ complications resulting in cirrhosis and end-stage renal disease (ESRD) requiring organ transplantation. Additionally, the risk of premature death due to cardiovascular disease was high in these patients.

Definitions

Cumulative survival in period t is defined as the proportion of the original NIH Follow-Up Study sample who are still alive, and conditional (or per-period) survival in period t as the probability of surviving to period t+1 conditional on having lived until period t. A sequence of conditional survival probabilities determines a sequence of cumulative probabilities, and vice-versa.

Survival is evaluated with respect to the time elapsed from the beginning of the trial, but does not depend on a patient's age. Cumulative survival in period t is best interpreted as the probability that a patient of average initial sample age plus t years is alive.

It is assumed that survival in period t is determined by the number of impaired organs that a patient has in period t. However, the length of time that a patient has experienced impairment is not considered. That is, a patient who begins the trial with impairment to two of their organs (and does not experience additional impairment) is assumed to face the same survival odds five years after the start of treatment as another patient who develops impairment to their second order in the fifth year. This assumption simplifies the analysis considerably, since only the current number of impaired organs each patient has developed is required to be tracked. As a result, however, the mortality risk of patients who live with impaired organs for a longer time may be underestimated, and the mortality risk of patients with newly developed organ impairment could be overestimated. It is unclear whether this assumption makes our resulting survival curves more or less optimistic, but the magnitude of the effect is likely negligible.

Approach

It may be the case that mortality not only depends on the number, but also the identity of the impaired organs (impairment to the heart, for example, may be more consequential than impairment to a kidney). However, due to data limitations (a single-arm trial with114 patients (14 deaths)

[d], and a retrospective chart review with 178 (14 deaths)), only the number of impaired organs that a patient develops are considered. The relationship between organ impairment and mortality is modelled using only the natural history data.

The assumed relationship between mortality and the number of impaired organs is tested with a Cox proportional hazards model fit onto the natural history study data. The number of impaired organs as a time-varying covariate is included in the model to predict mortality. This yields a positive, significant coefficient, detailed in Table 73.

Table 73: Cox Proportional Hazards Model on GL/PL Study with Number of Impaired Organs as Time-varying Covariate.

Independent Variable	Regression Coefficient (Beta)	Exponential of Regression Coefficient (Hazard Ratio)	Standard Error	p-value
FULL SAMPLE				

[d]While the trial was conducted for 114 patients (14 deaths), our analyses are restricted to 112 patients (12 deaths), due to a lack of data for two of the study patients: patient 25 dies 2.4 months after the start of the trial, whereas there is a lack any clinical information for patient 47.

Number of Impaired Organs	1.2839*	3.6108	0.3329	0.000115
GL SAMPLE				
Number of Impaired Organs	1.0897*	2.9734	0.4155	0.00873
PL SAMPLE				
Number of Impaired Organs	1.5237*	4.5892	0.5302	0.00406
*Statistically significant at 1%				

Testing of proportional hazards assumptions

The Cox model assumes that the hazard rates of groups of patients are related in a proportional manner that is constant over time, which allows for estimation of a constant scaling coefficient. For example, suppose that the hazard of dying among males in a population is twice as high as that of females. A Cox model regression on these data would yield a positive coefficient for a dummy variable indicating that the patient is male, the exponential of which would be 2. This relative hazard ratio of 2 should hold over time if the proportional hazards assumption is met. The assumption of proportionality can be tested with a Schoenfeld residual test, and hence is used to test groups of patients composed of those with a particular number of impaired organs.

The Schoenfeld residuals are defined as follows:

$$r_i = Z_i(T_i) - \bar{Z}(T_i; \hat{\beta}),$$

where *i* represents each individual, T_i is their time of death, $Z_i(T_i)$ is the observed number of impaired organs at death, and $\bar{Z}(T_i; \hat{\beta})$ represents the predicted number of impaired organs at death, given a Cox coefficient of $\hat{\beta}$. The Schoenfeld residual is thus the difference between the observed covariate value and the predicted value given the included covariates at the time of death. If the proportional hazards assumption holds, there should be independence between the Schoenfeld residual and time; therefore, the slope of a best-fit line through plotted residuals against time of death (r_i vs T_i) should be approximately 0.

The Schoenfeld residual test results for the coefficient on the number of impaired organs are summarised in Table 74. Based on the three tests for each correlation coefficient between the transformed t and scaled Schoenfeld residual, there is insufficient statistical evidence to reject the null hypothesis that the slope is approximately 0; therefore, this concludes that there is no statistically significant correlation between time and the Schoenfeld residuals, showing that the proportional hazards assumption is valid for each patient subset.

Table 74: Schoenfeld residual test results

Patient type	Correlation coefficient between transformed t and scaled Schoenfeld residual	Chi-square	p-value
GL patients	0.11	0.0121	0.912
PL patients	0.0937	0.039	0.844
All patients	-0.136	0.192	0.661

Sensitivities

The robustness of these finding is tested by including additional covariates in the baseline model, such as gender, country of origin, age, and lab values (Hemoglobin A1C, triglycerides levels, and leptin levels). The results can be found in Table 75.

Model 1 includes squared and cubed versions of the main independent variable - number of impaired organs. This allows testing for non-linear effects of this variable on mortality. Model 2 includes demographic covariates such as age, gender and country of origin, thereby testing for any significant effects of these characteristics on mortality. Model 3 includes values of hemoglobin A1C, triglycerides, and leptin as covariates in order to test the effects of these indicators on mortality. Finally, model 4 tests the robustness of our Cox model by including both demographic and laboratory data as covariates. Overall, our results show that the coefficient on the number of impaired organs retains its significance (except for model 1), while none of the above covariates yield significant coefficients at standard levels.

Table 75: Cox Proportional Hazards Model on GL/PL Study with additional covariates.

Independent Variable	Regression Coefficient (Beta)	Exponential of Regression Coefficient	% increase (+ve) or decrease (-ve) in risk	Standard Error	p-value
FULL SAMPLE					
Model 1					
Number of Impaired Organs	3.93667	51.24774	+5025%	3.68263	0.285
Squared Number of Impaired Organs	-0.38949	0.67740	-32%	2.01964	0.847
Cubed Number of Impaired Organs	-0.06185	0.94002	-6%	0.34090	0.856
Model 2					
Number of Impaired Organs	1.7035861*	5.4936126	+439%	0.3846092	<0.0001
Age	0.0004888	1.0004890	0%	0.0228490	0.983
Gender	0.1937144	1.2137496	+21%	0.6550882	0.767
Country	-0.5334388	0.5865843	-41%	0.6808295	0.433
Model 3					
Number of Impaired Organs	1.873749*	6.512670	+551%	0.363060	<0.0001
Hemoglobin A1C lab	-0.261286	0.770061	-23%	0.432365	0.546

Triglycerides lab	-0.001798	0.998204	0%	0.001810	0.321
Leptin lab	-0.232359	0.792661	-21%	0.246952	0.347
Model 4					
Number of Impaired Organs	2.017188*	7.517155	+652%	0.465604	<0.0001
Age	-0.004775	0.995236	0%	0.025004	0.849
Gender	0.350113	1.419228	+42%	0.686823	0.610
Country	-0.742169	0.476080	-52%	0.765326	0.332
Hemoglobin A1C lab value	-0.168343	0.845064	-15%	0.493977	0.733
Triglycerides Lab	-0.002167	0.997835	0%	0.001836	0.238
Leptin Lab	-0.266450	0.766094	-23%	0.266053	0.317
GL SAMPLE					
Model 4					
Number of Impaired Organs	1.871142	6.495709	+550%	0.823224	0.0230
Age	-0.029539	0.970893	-3%	0.061317	0.6300
Gender	2.327878	10.256154	+926%	1.292819	0.0718
Country	-3.117316	0.044276	-96%	1.659819	0.0604
Hemoglobin A1C lab value	-0.264345	0.767709	-33%	1.560951	0.8655
Triglycerides Lab	-0.006280	0.993739	0%	0.005714	0.2717
PL SAMPLE					
Model 4					

Number of Impaired Organs	2.1243346	8.3673280	+737%	0.8921632	0.0173
Age	0.0044091	1.0044188	0%	0.0432232	0.9188
Gender	-0.7081594	0.4925499	-51%	1.1823639	0.5492
Country	-0.6376429	0.5285368	-47%	1.8004896	0.7232
Hemoglobin A1C lab value	-0.5219081	0.5933872	-41%	0.7628192	0.4939
Triglycerides Lab	-0.0002665	0.9997335	0%	0.0029271	0.9275
Leptin Lab	-0.2794411	0.7562062	-24%	0.3537236	0.4295
*Statistically significant at 1%					

Organ abnormality specific survival curves

The model relies on survival curves derived from the data to predict the probability that a particular patient is alive in any one period. To construct these survival curves, baseline GL and PL survival curves obtained from the NIH Follow-Up data and from the UK population life table respectively as described in section 17.6.2.2, are scaled by the coefficient obtained from the Cox model described in Table 73, above. The GL baseline survival curve is interpreted as the survival of patients with the average number of impaired organs among GL patients in the NIH Follow-Up study; the PL baseline survival curve is interpreted as the survival of patients with the average number of impaired organs among PL patients in the NIH Follow-Up study. For both GL and PL patients, we first derive the survival curve for patients with 0 impaired organs; then, we scale the survival curve of 0 impaired organs by the Cox model coefficient to derive the survival curves for patients with 1, 2, 3, and 4 impaired organs. This yields five survival curves, one corresponding to each of the possible levels of organ impairment – 0, 1, 2, 3, and 4. These curves for the GL and PL patients are shown in Figure 40and

Figure 41 respectively.

Figure 40: GL survival curves by organ impairment levels

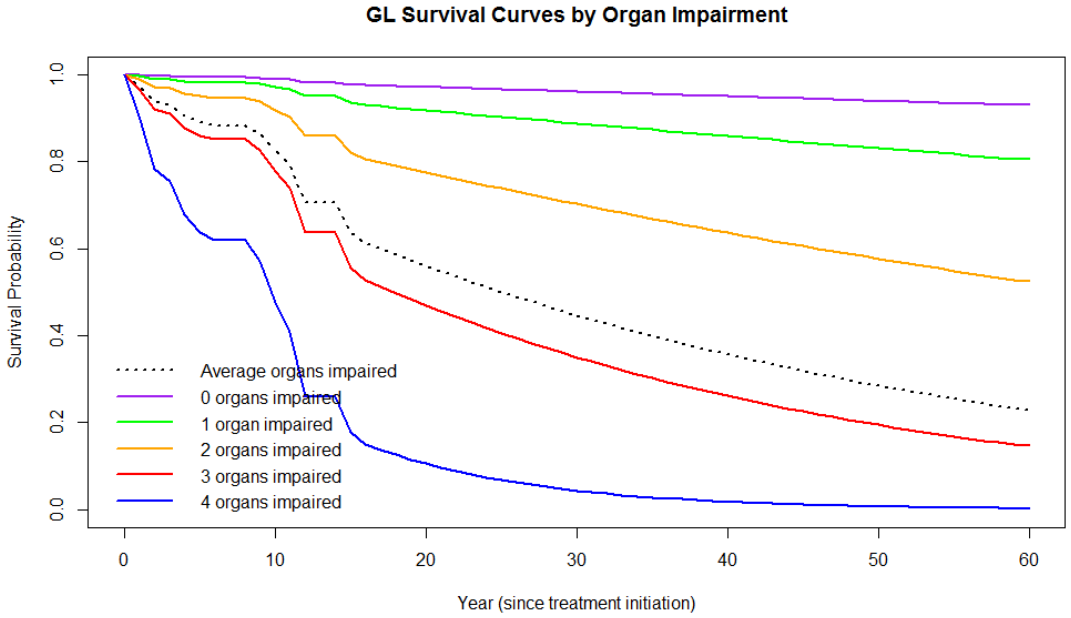
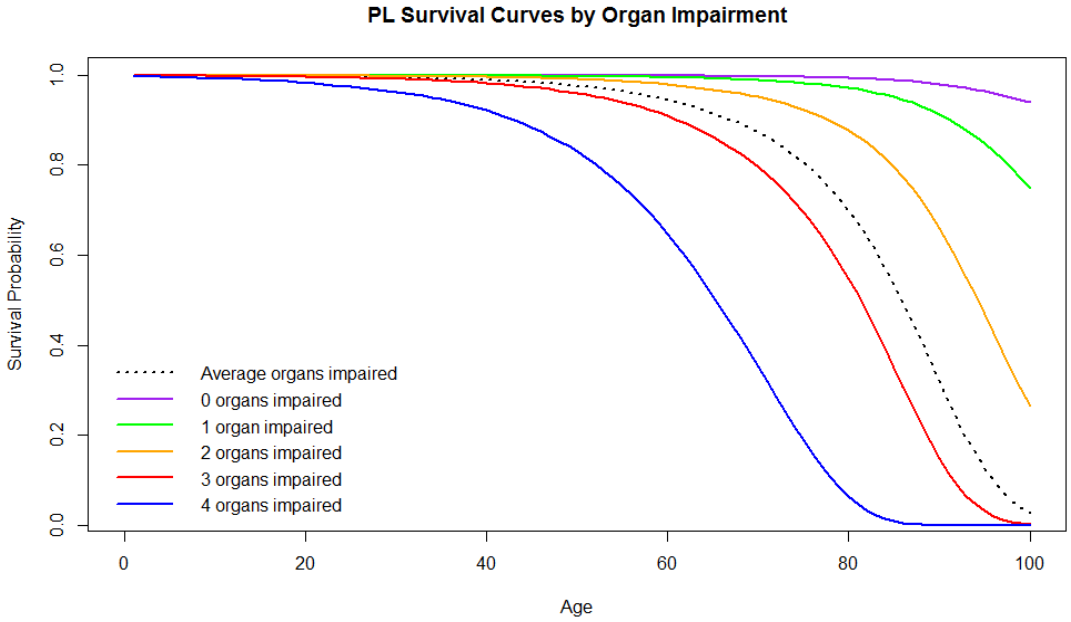


Figure 41: PL survival curves by organ impairment levels



17.6.2.4 Effect of metreleptin treatment on organ damage and mortality

The results described in section 17.6.2.4 suggest that organ abnormalities progress more quickly for patients in the natural history study than in the NIH follow-up study. As patients in the later study are treated with metreleptin, it is posited that metreleptin use accounts for some, or all of, this difference. Likewise, as organ abnormality progression is associated with increased mortality, use of metreleptin may also reduce premature mortality. To quantify this effect, two approaches are pursued:

1) Adjustment for differences in patient characteristics between the studies via a matching approach followed by cox proportional hazard model that includes treatment as a characteristic

2) Simulation of counterfactual organ abnormality progression and subsequent mortality for patients observed in the NIH study had they not received metreleptin

Data from the NIH Follow-Up Study is used for the sample of treated patients. Untreated patient data comes from the natural history study. However, as Table 76 shows, the demographic characteristics of patients included in the analyses differ between the two studies, motivating the need for one of these two approaches.

Table 76: Demographic characteristics of treated patients in NIH Follow-Up Study and untreated patients in GL/PL Study

	N	Mean/%	N	Mean/%
	GLPL Patients		NIH Study Patients	
Number of patients	178		112	
Mean age at first symptoms		21.1		13.3*
Age at Metreleptin Initiation		N/A		24.3
GL		N/A		17.6
PL		N/A		34.7
Gender				
Male (%)	59	33.15	19	16.96
Female (%)	119	66.85	93	83.04
Country of Origin				
USA	98	55.06		
Turkey	80	44.94		
Lipodystrophy Type				
GL	56	31.46	68	60.71
PL	122	68.54	44	39.29
Speed of Organ Abnormality Progression (# of abnormalities / age at trial start)**				
GL	35	0.044	68	0.142
PL	74	0.0127	44	0.073

*3 patients have date of first symptom to be prior to birth. For these, it is assumed that symptoms were first seen at birth.

**Speed of progression for natural history patients is evaluated for GL patients at age 17.6 and at age 34.7 for PL patients. There are fewer patients in this section due to attrition over the course of the study (from birth until the relevant reference age).

Matching Methodology

Patients in the untreated sample have, on average, symptoms that are less severe and experience slower progression than treated patients. This makes it difficult to conduct a straightforward comparison of the two groups. Instead, pairs of patients were matched between the two studies. For each treated patient, an untreated patient at a particular age, whose level of organ abnormality at that age is close to the treated patient's and whose reference age matches the treated patient's age at the start of treatment, was found to match. Some weight was also assigned to gender, so that patients of the same gender are more likely to be matched to one another. The flexible approach allows weighting of age, level of organ abnormality and gender to differ, which changes the relative importance of each characteristics for the measure of distance between treated and untreated patients.

Only GL patients to GL patients were matched, and the same for PL patients. An algorithm searches through each GL/PL patient's many pseudo-patients (those generated by specifying some reference age) for the one who minimises this distance, then matches the two. In this manner, every treated patient was matched with one pseudo-patient from the untreated sample, while a single untreated patient

may contribute many pseudo-patients. The objective function that is minimised for each patient is the following:

Diff: (Absolute difference between the treated and untreated individuals) / (Standard deviation of the absolute difference between the treated and untreated individuals)

Gender: I(Gender = Male) = 1

α * Diff(Age) + **β** * Diff(Initial Organ Damage) + (**1** - **α - β)** * Diff(Gender)

Description of Matched Cohort

The matching approach results in a list of pairs of treated patients and untreated pseudo-patients. The sample statistics of the two can be found below, in Table 77.

Table 77: Sample statistics of treated and matched untreated pseudo-patients

	Treated (NIH)	**Untreated (matched GL/PL)**
Age at first symptoms (mean)	13.33	13.94
Age at start of treatment (mean)	24.28	25.51
Number of impaired organs at start of treatment (mean)	2.52	2.36
Number of mortality events (count)	13	31
% male	16.96	16.96

Modelling organ progression for matched untreated patients

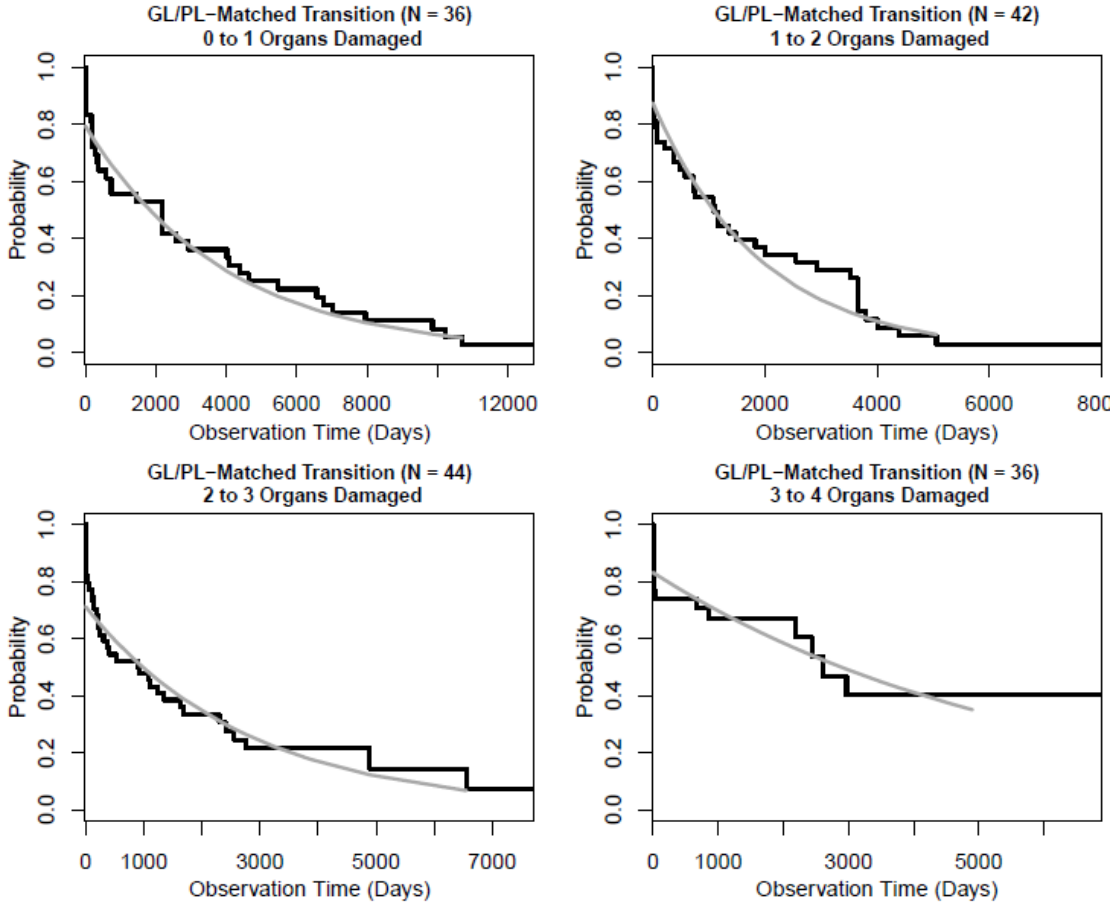
In a bid to estimate progression probabilities for patients who are comparable to our treated sample, treated patients were matched to those in the natural history study and derive the latter's organ abnormality progression probabilities through the same methods described above. Intuitively, a natural history patient is searched for who achieves the same level of organ abnormality as a candidate treated patient at around the same age. In this fashion, a single natural history patient may prove to be a match for a number of treated patients, and may match at different reference ages.

In this section, those patients who contributed pseudo-patients to the match generated by setting α=β=0.35 are studied. Using only this subset of (full) natural history patients, progression probabilities are generated for transitions from 0 to 1, 1 to 2, 2 to 3, and 3 to 4 organs with abnormalities. The results are summarised in Table 78, and the curves are fitted in order to derive these probabilities in the graphs that follow. This exercise allows the consideration of those untreated patients who are most similar to the treated sample and study their organ progression trajectory from birth. The objective is to use these estimated transition probabilities as counter-factual values for what would have been generated by treated patients, had they never received metreleptin.

Table 78: Estimated progression probabilities for matched natural history patients (N=47)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	8.9%	36	36
1 to 2	17.3%	42	39
2 to 3	12.3%	44	36
3 to 4	6.2%	36	16

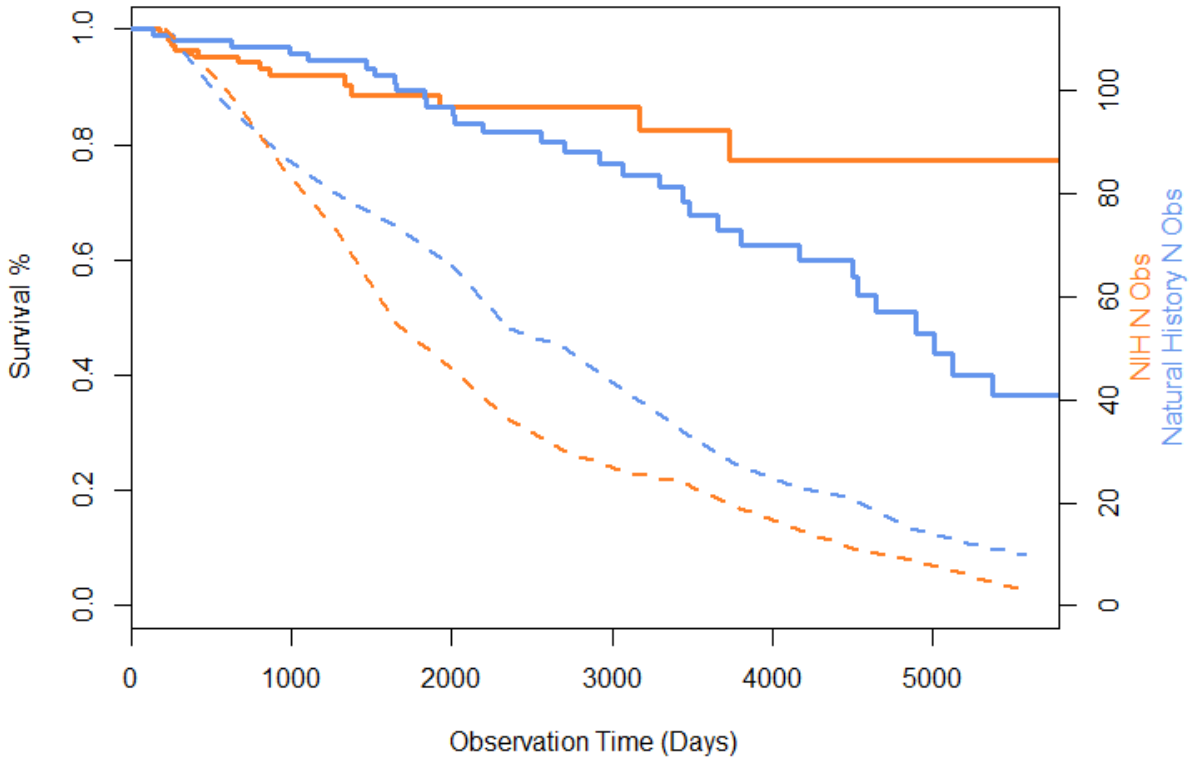
Figure 42: Organ abnormality progression among matched natural history patients



Estimating survival benefit of treatment

Comparison of the cumulative survival of treated and matched natural history cohorts suggests that there is a survival benefit of metreleptin. This can be easily gleaned from the graph in Figure 43, and the following analyses are set out to confirm, or disprove, this hypothesis.

Figure 43: Cumulative survival KM curves for NIH study and matched Pseudo patients



Having matched our samples, a Cox proportional hazards model is estimated with a treatment dummy (that takes a value of 1 for all patients in the NIH Follow-Up study) to evaluate the effect of treatment on mortality, when the two samples are similar.

Since natural history patients contribute multiple observations, standard errors at the patient level are clustered. The results are suggestive – the matching weights (such as 35% weight on age, 35% weight on the level of organ abnormality at treatment initiation and 30% on gender) yield negative Cox coefficients with p-values slightly above the 0.1 threshold. Negative coefficients indicate that treatment decreases the risk of mortality. With the preferred matching weights (35-35-30), the effect translates into a 41.4% decrease in the risk of mortality, albeit with a p-value equal to 0.192. Results of the various models run are included in Table 79 below:

Table 79: Results of Cox model regressions on a treatment dummy

Matching weights (age – organ damage – gender)	Exp(Coefficient)	Clustered standard errors?	p-value
45 – 45 – 10	0.6263	Yes	0.216
45 – 45 – 10	0.6263	No	0.149
40 – 40 – 20	0.5843	Yes	0.194

40 – 40 – 20	0.5843	No	0.107
35 – 35 – 30	0.5859	Yes	0.192
35 – 35 – 30	0.5859	No	0.110
30 – 30 – 40	0.5859	Yes	0.192
30 – 30 – 40	0.5859	No	0.110

17.6.3 Conclusions and use of these analyses

The economic model draws from these analyses extensively to model organ abnormality progression and subsequent mortality. For metreleptin treated patients, organ abnormality progression after the end of real-world data proceeds according to the transition probabilities in Table 70. For standard of care patients, organ abnormality progression proceeds according to the transition probabilities in Table 78. In both cases, conditional survival probabilities (described in section 17.6.2.3) that correspond to the number of organ abnormalities during the period are applied, drawing from the appropriate GL or PL survival curves.

Although the direct analysis of the effect of metreleptin treatment on mortality described in section 17.6.2.4 is suggestive and intriguing, unfortunately the sample size is insufficient for our approach to yield a significant coefficient. In light of this, the more robust relationship between organ abnormalities and mortality (described in section 17.6.2.3) is used to predict mortality in the model.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Metreleptin for treating lipodystrophy

[ID861]

Additional evidence

Specification for company submission of evidence

29 March 2018

Contents

OVERVIEW

Due to the anticipated change in label indication, we are providing an update to all Cost Effectiveness model results (sections 12.5, 12.6, and 12.8). A brief description of the label indication and the changes to the model are included in an addendum dated 29th March 2018. These results also incorporate changes to the model base case described in our response documents dated 27th February and 02nd March 2018. We have additionally submitted an updated to the PAS template that also reflect these changes and a full Excel model.

12 Economic analysis (Updated March 29, 2018)

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.5 Results of economic analysis

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

The following presents the base case incremental results comparing metreleptin to SoC over a 90-year time horizon, assuming availability of vials for the 2.5mg, 5mg, and 10mg doses of metreleptin at list price. The results of the base-case ICER with the patient access scheme are presented in a separate document (refer to the HST PAS Evidence Submission).

Table D1: Cost-effectiveness results for label indication group for 10mg dose (Base case 1)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (90 years)			
Cost of Therapy(£)	£11,171,095	£48,695	£11,122,400
Other Medical Costs(£)	£28,070	£26,159	£1,911
Total Costs (£)	£11,199,165	£74,854	£11,124,311
Treatment effectiveness per patient (90 years)			
Life Years (Years)	19.18	16.23	2.95
Utility Decrements (QALYs)	-10.84	-15.65	4.82
Quality-Adjusted Life Years (QALYs)	8.34	0.58	7.77
Cost-effectiveness (90 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			£1,432,391

Table D2: Cost-effectiveness results for label indication group for multiple vials (Base case 2)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (90 years)			
Cost of Therapy(£)	£5,721,224	£48,695	£5,672,529
Other Medical Costs(£)	£28,070	£26,159	£1,911
Total Costs (£)	£5,749,294	£74,854	£5,674,440
Treatment effectiveness per patient (90 years)			
Life Years (Years)	19.18	16.23	2.95
Utility Decrements (QALYs)	-10.84	-15.65	4.82
Quality-Adjusted Life Years (QALYs)	8.34	0.58	7.77
Cost-effectiveness (90 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			£730,654

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-

over). Please use the following table format for each comparator with relevant outcomes included.

The outcomes from the model were not compared with the clinical trial results as no randomised controlled trial of metreleptin in lipodystrophy patients has been conducted, largely due to the extreme rarity and severity of the condition.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

This does not apply to the individual patient model.

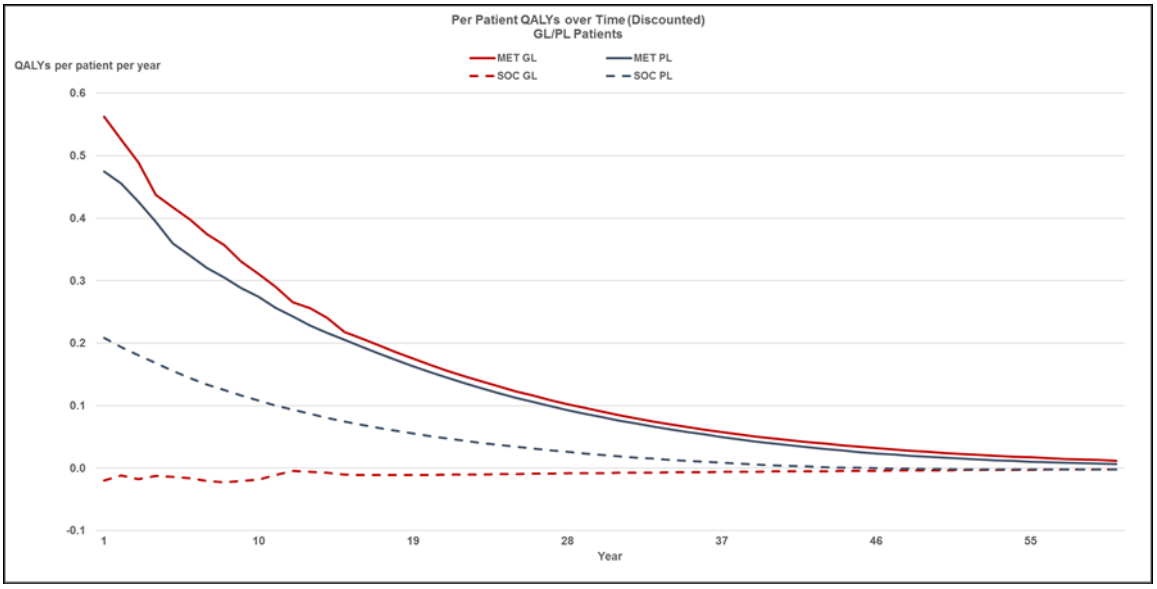
12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALYs accrue to patients on a per-period basis over the course of 90 one year periods. A patient's attribute profile in each period generates a QALY decrement that is subtracted from 1–the utility from perfect health. QALYs are then summed across all periods in the model, with each period's QALY value discounted appropriately. QALYs are also scaled by the survival probabilities of patients. Since attribute impairment is stochastic, QALY decrements arise with some likelihood in each period and are scaled by the appropriate probability.

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

In the model, LY and QALYs accrue over a period of 90 years. The per patient QALYs over time are presented in Figure D1.

Figure D1: Per Patient QALYs over Time (Discounted) (BC1 and BC2)



12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

The figures below display each associated health condition's incremental impact on period 1 QALYs for metreleptin and SOC patients. Overall, an average metreleptin patient will experience a year of life equivalent to nearly half of one lived in perfect-health while the average standard of care patient will experience a year of life equivalent to nearly one-third of one lived in perfect-health and about three-fifths of one lived while treated with metreleptin. While the assumption that a lipodystrophy patient with none of the specified attributes would experience perfect health is unrealistic, subtracting the utility decrements from a lower base results in a number of standard of care patients receiving negative utility. The difference in per period utility between metreleptin treated and standard of care patients does not depend on the value assigned to perfect health, the choice to not adjust the QALY base seems reasonable.

Figure D2: Utility decrements in period 1 (MET patients) (BC1 and BC2)

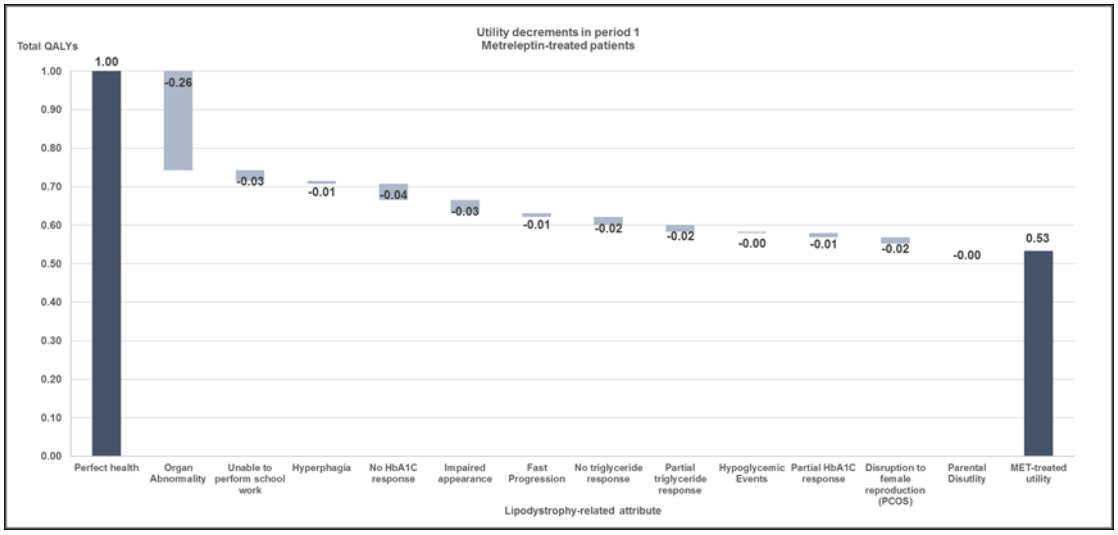
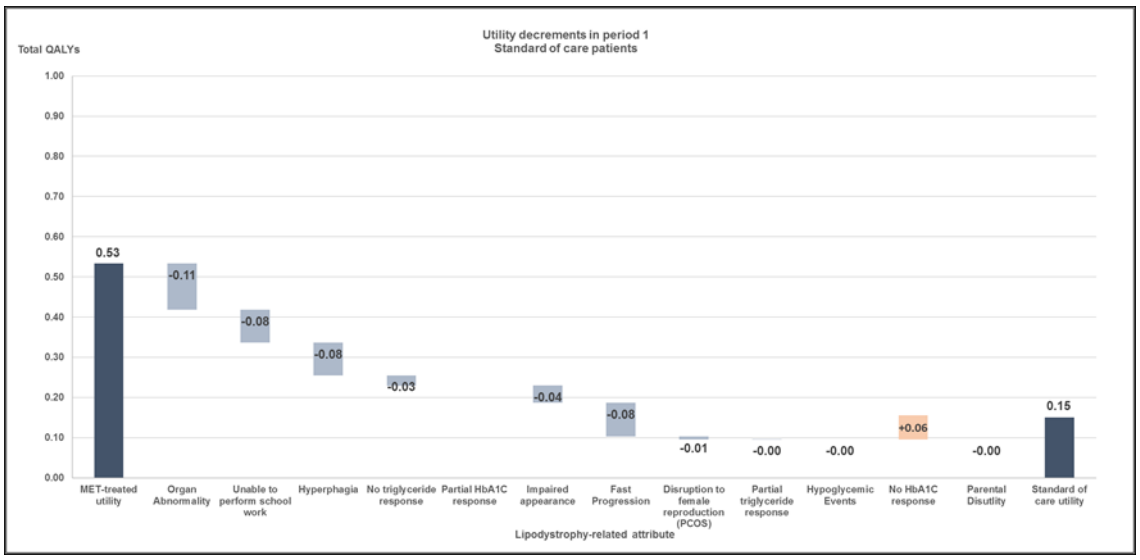


Figure D3: Utility decrements in period 1 (SOC patients) (BC1 and BC2)



12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table D3: Undiscounted incremental QALYs for label indication group (BC1 and BC2)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Treatment effectiveness per patient (90 years)			
Life Years (Years)	41.33	33.07	8.25
Utility Decrements (QALYs)	-25.06	-32.80	7.74
Quality-Adjusted Life Years (QALYs)	16.27	0.27	15.99

12.5.8 Please provide undiscounted incremental costs for the intervention compared with each comparator

Table D4: Undiscounted costs for label indication group for 10mg dose (BC1)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Treatment effectiveness per patient (90 years)			
Cost of Therapy	£20,591,763	£99,223	£20,492,540
Other Medical Costs	£65,666	£56,138	£9,528
Total Costs	£20,657,429	£155,362	£20,502,068

Table D5: Undiscounted costs for label indication group for multiple vials (BC2)

Metreleptin vs.SOC	Metreleptin	SOC	Increment
Treatment effectiveness per patient (90 years)			
Cost of Therapy	£10,554,765	£99,223	£10,455,542
Other Medical Costs	£65,666	£56,138	£9,528
Total Costs	£10,620,431	£155,362	£10,465,069

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Not applicable.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Not applicable.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in Error! Reference source not found.**.**

The results of the deterministic sensitivity analysis are presented in

Figure D4 and Figure D5.

Figure D4: DSA one-way results for 10mg dose (based around BC1)

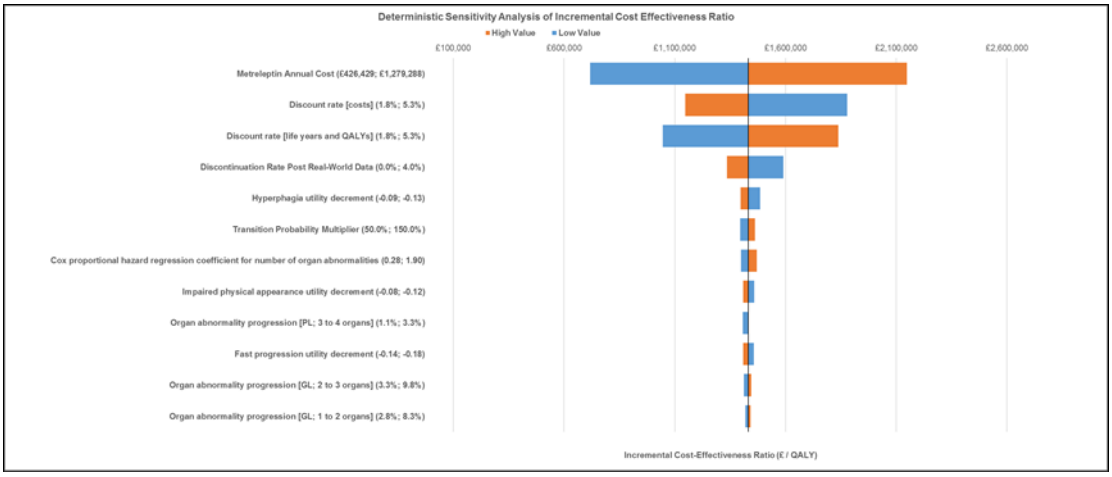
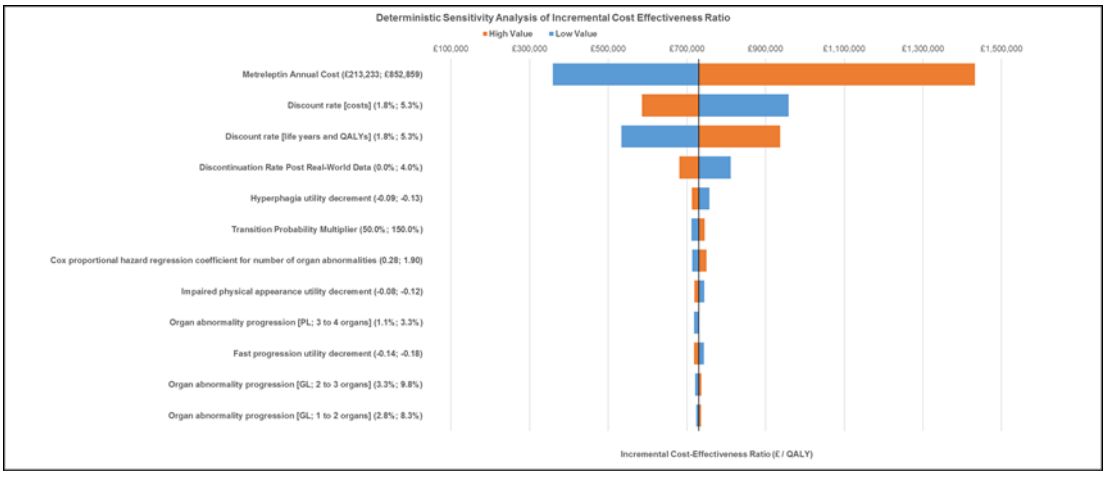


Figure D5: DSA one-way results for multiple vials (based around BC2)



12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in Error! Reference source not found..

The deterministic multi-way scenario implements the following changes to the base case for the label indication group:

- Reduces the list price by [redacted]
- Doubles the hyperphagia decrement to -0.22
- Incorporates resolution of heart abnormalities for some patients who experience a resolution of hypertension

Table D6: DSA multi-way scenario results for 10mg doses (based around BC1)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (90 years)			
Cost of Therapy(£)	[redacted]	£48,822	[redacted]
Other Medical Costs(£)	£27,334	£26,203	£1,131
Total Costs (£)	[redacted]	£75,025	[redacted]
Treatment effectiveness per patient (90 years)			
Life Years (Years)	19.35	16.27	3.08
Utility Decrements (QALYs)	-10.86	-17.09	6.23
Quality-Adjusted Life Years (QALYs)	8.49	-0.81	9.30
Cost-effectiveness (90 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			[redacted]

Table D7: DSA multi-way scenario results for multiple vials (based around BC2)

Metreleptin vs. SOC	Metreleptin	SOC	Increment
Costs per patient (90 years)			
Cost of Therapy(£)	[redacted]	£48,822	[redacted]
Other Medical Costs(£)	£27,334	£26,203	£1,131
Total Costs (£)	[redacted]	£75,025	[redacted]
Treatment effectiveness per patient (90 years)			
Life Years (Years)	19.35	16.27	3.08
Utility Decrements (QALYs)	-10.86	-17.09	6.23
Quality-Adjusted Life Years (QALYs)	8.49	-0.81	9.30
Cost-effectiveness (90 years)			
Incremental Cost-effectiveness ratio (£ per QALY)			[redacted]

12.5.13 Present results of the probabilistic sensitivity analysis described in Error! Reference source not found..

Figure 6: Scatterplot PSA results for multiple vials (BC2)

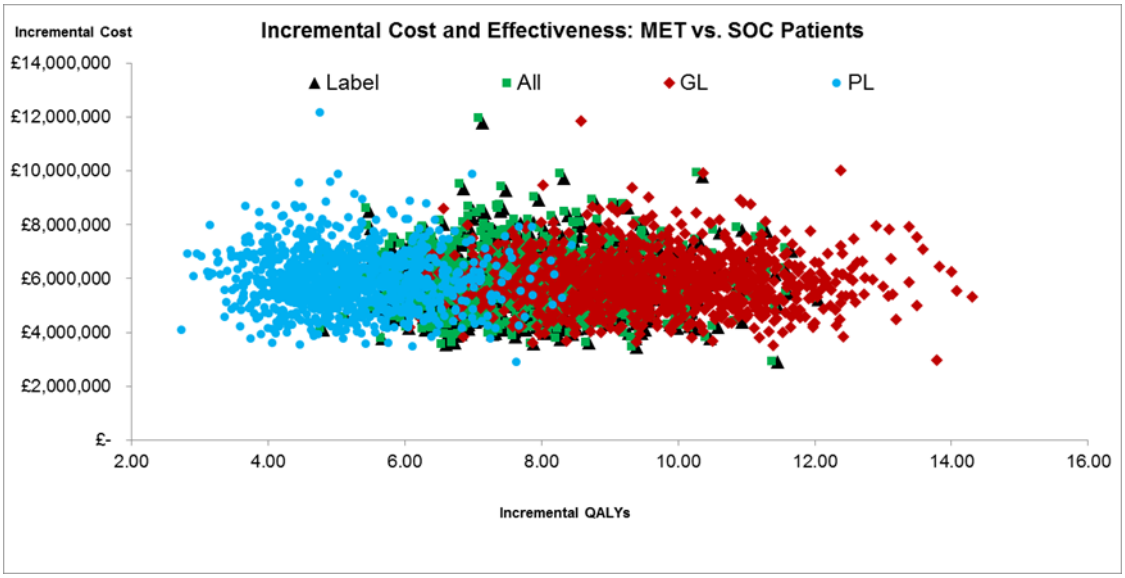
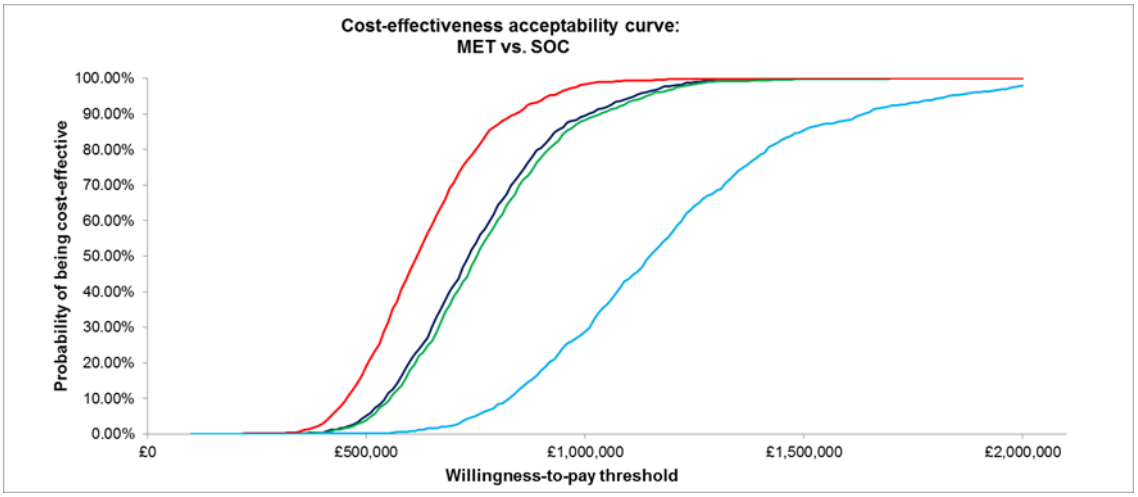


Figure 7: Cost-effectiveness acceptability curve for multiple vials (BC2)



12.5.14 What were the main findings of each of the sensitivity analyses?

The ICER and QALYs vary as expected as price and utility decrements are varied. While the range of QALYs is significant metreleptin is associated with significant QALY gain in all scenarios as seen in Table D9.

Table D8: Scenario analysis results for 10mg dose (BC1)

Structural Scenario	Specific Assumptions/Inputs	ICER	QALYs Gained
Base case	List price	£1,432,391	7.77
Base case plus assume [redacted] lower price for metreleptin	List price with [redacted], with one vial	[redacted]	7.77
Base case plus alternate inputs	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	£1,206,039	9.30
Base case plus alternative inputs assume [redacted] lower price for metreleptin	List price with [redacted] discount, with multiple vial sizes, doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	[redacted]	9.30
Future Price Changes: Loss of metreleptin exclusivity	Metreleptin list price falls 90% after 10 years	£780,563	7.77
Elimination of mortality benefit of metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ abnormality.	£1,438,784	7.77
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	£1,461,201	7.54
	all organ progression probabilities decreased by 50%	£1,394,490	8.05
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	£1,386,054	8.02
Alternate survival extrapolation methods: GL curve parameterization	Weibull	£1,409,130	8.05
	Log Normal	£1,418,599	7.93
	Logit	£1,430,755	7.78
Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	£1,398,821	7.84
	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	£1,469,591	7.59

Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	£1,379,112	7.48

Table D9: Scenario analysis results for multiple vials (BC2)

Structural Scenario	Specific Assumptions/Inputs	ICER	QALYs Gained
Base case	List price, with multiple vial sizes	£730,654	7.77
Base case plus assume [redacted] lower price for metreleptin	List price with [redacted], with multiple vial sizes	[redacted]	7.77
Base case plus alternate inputs	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	£615,167	9.30
Base case plus alternative inputs and assume [redacted] lower price for metreleptin	List price with [redacted], with multiple vial sizes, doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	[redacted]	9.30
Future Price Changes: Loss of metreleptin exclusivity	Metreleptin list price falls 90% after 10 years	£398,469	7.77
Elimination of mortality benefit of metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ abnormality.	£733,848	7.77
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	£745,356	7.54
	all organ progression probabilities decreased by 50%	£711,266	8.05
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	£707,002	8.02
Alternate survival extrapolation methods: GL curve parameterization	Weibull	£718,763	8.05
	Log Normal	£723,623	7.93
	Logit	£729,827	7.78
	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	£713,389	7.84

Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	£749,796	7.59
Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	£703,720	7.48

12.5.15 What are the key drivers of the cost results?

The key cost drivers in the individual patient model are the annual price of Metreleptin, the discount rate applied to treatment costs as well as patient life years and QALYs, and the utility decrement associated with hyperphagia. As depicted in the above deterministic sensitive analysis, however, many variables, especially those related to utility decrements and probabilities of increased organ abnormality, have an incremental impact on the ICER estimate.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

The results of the preliminary analysis of early initiation, described in 12.4.1, are not described elsewhere and are shown in

Table D10 below.

Table D10: Early treatment initiation at age 1 results (CGL)

Structural Scenario	Specific Change	ICER	QALYs Gained
Early treatment initiation at age 1: CGL	List price, multiple vial sizes (No Discount)	865,667	12.35
	List price, multiple vial sizes plus double hyperphagia decrement, plus parental disutility of -0.05 per period	736,750	14.51

12.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

Subgroups included in the model were identified based on the labelled indication. The following subgroups were included:

- Generalised lipodystrophy meeting labelled indication (GL) (n=63)
- Partial lipodystrophy patients meeting labelled indication (PL) (n=17)
- All NIH patients (n=112), including those who do not meet the labelled indication
- Congenital generalised lipodystrophy, including those who do not meet the labelled indication (CGL) (n=48)

12.6.2 Define the characteristics of patients in the subgroup(s).

Lipodystrophy may be either congenital (inherited) or acquired and may be generalised (affecting adipose tissue throughout the body) or partial, affecting adipose tissue in parts of the body. While heterogeneous in aetiology and manifestation, metabolic abnormalities, progressive abnormality to organs, hypoleptinaemia (low leptin), and favourable response to metreleptin are commonly observed across patients.

The severity and burden of lipodystrophy is consistently high among patients with generalised lipodystrophy (GL). The GL subgroup is consistent with the labelled

indication, patients with congenital or acquired GL, in adults and children 6 years of age and above.

The presentation of partial lipodystrophy (PL) is more heterogeneous, with some patients exhibiting more severe metabolic complications. The indication being sought within PL includes the group of patients with more severe metabolic abnormalities regardless of standard treatment and lower leptin levels. The PL subgroup is consistent with the labelled indication, patients with familial or acquired PL, characterised by leptin level < 12 ng/ml with triglycerides > 500 mmol/l and/or HbA1c > 8 %, in adults and children 12 years of age and above uncontrolled on standard therapy.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

The subgroup analysis is conducted by restricting the results from the model to those associated with only patients who meet the subgroup criteria. For instance, in the GL subgroup analysis, only patients who met the label indication and who had GL were included, so the model results were averaged across these 63 patients rather than all 80 patients who met the label indication.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Table D11: Discounted subgroup results for 10mg dose (BC1)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	19.31	16.39	8.44	0.74	-0.42	-0.85	£1,466,610
GL	68	17.98	13.61	8.89	-0.52	-0.38	-0.91	£1,200,597
PL	44	21.37	20.69	7.74	2.68	-0.49	-0.76	£2,230,285
CGL	48	19.27	14.77	9.59	-0.91	-0.39	-0.96	£1,168,008

Table D12: Undiscounted subgroup results for 10mg dose (BC1)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	41.91	33.71	16.55	0.69	-0.44	-0.88	£1,320,842
GL	68	39.20	26.81	17.75	-1.41	-0.39	-0.94	£1,087,934
PL	44	46.10	44.37	14.70	3.93	-0.51	-0.78	£1,961,275
CGL	48	42.88	29.79	19.49	-2.17	-0.40	-0.99	£1,050,962

Table D13: Discounted subgroup results for all vial sizes (BC2)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	19.31	16.39	8.44	0.74	-0.42	-0.85	£748,091
GL	68	17.98	13.61	8.89	-0.52	-0.38	-0.91	£612,669
PL	44	21.37	20.69	7.74	2.68	-0.49	-0.76	£1,136,864
CGL	48	19.27	14.77	9.59	-0.91	-0.39	-0.96	£595,952

Table D14: Undiscounted subgroup results for all vial sizes (BC2)

Subgroup	Number of patients per arm	Life years		QALYs		Utility decrements (period 1)		Cost per QALY
		MET	SOC	MET	SOC	MET	SOC	
All patients	112	41.91	33.71	16.55	0.69	-0.44	-0.88	£674,180
GL	68	39.20	26.81	17.75	-1.41	-0.39	-0.94	£555,736
PL	44	46.10	44.37	14.70	3.93	-0.51	-0.78	£999,867
CGL	48	42.88	29.79	19.49	-2.17	-0.40	-0.99	£536,778

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

All subgroups identified are included in the submission.

12.8 Interpretation of economic evidence

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no published economic literature available on metreleptin in lipodystrophy patients.

Based on the results from this cost-effectiveness analysis, the ICER with PAS is a cost-effective use of NHS resources withjn the HST decision making criteria. This is due to a combination of large quantified QALY gain and unquantified direct and non-health benefits such as the broad impact on patients' and caregivers' lives (more detail in Section 14). Early intervention leads to substantial QALY gains and improved ICERs by preventing or slowing lipodystrophy's devastating progression. This is presented in an alternative model for base case patients with CGL starting

metreleptin treatment from Age 1. The incremental QALYs are found to be 12.35. These gains are due to the high benefit of preventing emerging organ abnormalities and progression of the disease in these patients. There is also a substantial level of unquantified health and non-health benefits such as improvements in the QoL of carers/family of children and adults with lipodystrophy.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

The model is based on patients from the US NIH, which represents a patient population that is different from the patients currently treated in the EAP in the UK. The US NIH patient data used in the model are more advanced patients than those currently treated in the EAP in England. Model sensitivities have illustrated that treatment in patients at less progressed stages of disease can provide greater QALY gains and high value and this is expected to be the case in England.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The model maximises transparency and flexibility as it follows real world observed patient level data and models individual patient's clinical experience and accruing costs and health benefits over time. Additionally, in extrapolating beyond the observed data, probabilities are used for each individual patient's development of organ abnormalities and resulting survival (and costs and utilities scaled accordingly) and in this sense the model leverages standard approaches from Markov models. Each individual patients can be thought of as a homogenous cohort in a Markov model with the overall results capturing the average across all patients. However, the model captures the heterogeneity of the underlying population and allows for history dependence in a manner that cannot be captured using a simpler structure. _ An alternate set of real world data, or different assumptions regarding the mix of baseline characteristics, could be used to further explore the relationship between metreleptin cost-effectiveness and characteristics of the treated population.

A weakness of the model is the lack of existing literature to provide model inputs specific to metreleptin use in lipodystrophy patients. The economic model structure using individual patient data is not as widely used as more familiar Markov methods and there are limited previous submissions using this modelling approach. There are clear limitations in the data that can be used as inputs to the economic model, as might be expected with such a rare condition. These include the following:

- There is a lack of data on the costs associated with lipodystrophy and the consequences of LD such as multiple organ abnormalities. The SLR showed there were no useful published estimates, hence a structured questionnaire for use with clinical experts was developed to derive resource use estimates for the symptoms and complications of LD. Interviews were conducted with two leading clinical experts based at Cambridge University Hospital. Unfortunately, they were unable to provide highly meaningful estimates due to

the very low numbers of patients treated and the great variation in patient profiles and resource utilisation across these patients, meaning it was difficult to provide typical, or 'on-average' estimates. The estimates in the model are based on a variety of sourcesbut are likely to underestimate the resource use reduction benefits of metreleptin as we have used conservative assumptions of cost in the absence of reliable data.

- The SLR indicated a lack of direct quality of life/PRO data for LD patients that could be useful for the economic model, or to assess the benefits of metreleptin, Hence, there was a need to conduct a separate DCE in order to quantify the HRQL benefits of metreleptin vs. SoC. However, as mentioned it is likely that the DCE as conducted in the general public has underestimated the HRQL impact of LD on patients, and also has not captured impact on caregivers.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Several further analyses are planned or already underway to further enhance the robustness/completeness of these results:

1) Earlier initiation of metreleptin treatment, prior to the development of substantial organ abnormalities, may substantially extend life and improve quality of life. A preliminary analysis using the economic model suggests that QALY gains may be upward of 12.1. However, additional work could be done to more rigorously extend the existing framework to allow more rigorous modelling of the likely economic impact of early treatment initiation

2) The improvement metreleptin treatment patients experience with regard to organ abnormalities reflected in the current model is based on laboratory values for liver and kidney (and -in the scenario analysis- hypertension resolution is used as a marker for improvement in heart abnormalities). However, the clinical trajectory of organ abnormalities included in the model (such as hepatomegaly and cardiomyopathy) can be more robustly documented with additional medical test results such as abdominal ultrasounds and echocardiograms. Additionally, further analysis of changes in the use of other medications may both add robustness to the current analysis of organ abnormality improvement and also support cost offsets not currently reflected in this model.

3) We acknowledge the patients from the NIH follow-up study may differ from patients seen in England. An effort is underway to collect data for patient in the United Kingdom participating in the early access programme (EAP) and these data can then be used with the existing model to directly estimate cost

Metreleptin for treating lipodystrophy ID861 - Addendum reflecting updated anticipated label

Submitted by Aegerion Pharmaceuticals Ltd.

Highly Specialised Technology Evaluation (HST)
National Institute of Health and Care Excellence

Submitted 29nd March 2018

1. Updated population

Aegerion currently anticipates that metreleptin will receive an EMA license for the following indication:

Metreleptin is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

- with confirmed congenital generalised LD (*Berardinelli-Seip syndrome*) or acquired generalised LD (*Lawrence syndrome*) in adults and children 2 years of age and above
- with specialist-confirmed familial partial LD or acquired partial LD (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

2. Changes to the economic model

The cost effectiveness model has been updated so that the "label indication" base case includes only patients who meet the criteria described above. Specifically, 3 patients who were treated with metreleptin at NIH did not meet the age restriction anticipated on the label and have been excluded from the "label indication" results. The resulting "label indication" group includes 109 patients (compared to 80 patients in our prior submission). Model results for the "label indication" group are similar to results for the full NIH population ("All patients"), with "label indication" patients gaining 7.77 QALYs from treatment (compared with 7.70 QALYs gained among all patients).

The "label indication" functionality within the model has also been updated to accommodate the new indication -- in the prior version of the model, the "label indication" functionality assumed that the label indication for PL would be more restrictive than the SPL subgroup and thus it was not possible to remove restrictions regarding maximum leptin levels and minimum HbA1c and triglyceride levels. This restriction has been removed and a programming error has been corrected. To further add transparency to the model, the patient baseline tab now indicates which specific patients are included in the "label indication" group.

We have updated all results from the cost effectiveness model to reflect the new "label indication" base case and are also providing the updated Excel model.

3. Note regarding confidentiality

We would also like to clarify that data from the NIH 991265/20010769 and FH101 clinical study reports provided as part of our earlier clarifications do not need to be treated as confidential, despite the confidential marking on the reports themselves.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Metreleptin for treating lipodystrophy ID861 - Addendum reflecting updated anticipated label

Patient Access Scheme submission template

29 March 2018

1 Introduction

Due to the anticipated change in label indication, we are providing an update to all Cost Effectiveness model results, including the PAS template. A brief description of the label indication and the changes to the model are included in an addendum dated 29th March 2018. These results also incorporate changes to the model base case described in our response documents dated 27th February and 02nd March 2018.

Base-case analysis

1.1 Please present in separate tables the economic results as follows.[1]

- The results for the intervention without the Patient Access Scheme
- The results for the intervention with the Patient Access Scheme

In this document the results for two alternative base cases (BCs) have been provided. BC1 represented the results at list price based on only a 10mg dose being licensed (at the time of marketing authorisation), and BC2 represented the results with the 2.5mg, 5mg and 10mg doses approved, which is expected within three months of marketing authorisation. These results are presented in Tables 1 and 2, and replicate those in the main submission document. Base case 3 and 4 are the equivalent results with the [redacted] PAS price discount applied (Table 3 and 4). Ultimately, within the time frame of this HST appraisal, BC4 is expected to become the only base case for decision making, as the three vials are fully expected to be approved, and assuming approval of the simple PAS submitted to PASLU.

[1] For outcome-based schemes, please see section 5.7 in appendix A.

Table 1: List price with only large vial available, with no discount (BC1)

	MET	SOC	Increment
Cost of Therapy (£)	£11,171,095	£48,695	£11,122,400
Other Medical Costs (£)	£28,070	£26,159	£1,911
Total Costs (£)	£11,199,165	£74,854	£11,124,311
Life Years	19.18	16.23	2.95
Utility Decrements (QALYs)	-10.84	-15.65	4.82
QALYs	8.34	0.58	7.77
QALYs (undiscounted)	16.27	0.27	15.99
ICER (£)			£1,432,391
Key: ICER: incremental cost-effectiveness ratio; LYG, life-year gained; MET, metreleptin; SOC, standard of care; QALY, quality-adjusted life year			

Table 2: List price with all vial sizes available (no discount) (BC2)

	MET	SOC	Increment
Cost of Therapy (£)	£5,721,224	£48,695	£5,672,529
Other Medical Costs (£)	£28,070	£26,159	£1,911
Total Costs (£)	£5,749,294	£74,854	£5,674,440
Life Years	19.18	16.23	2.95
Utility Decrements (QALYs)	-10.84	-15.65	4.82
QALYs	8.34	0.58	7.77
QALYs (undiscounted)	16.27	0.27	15.99
ICER (£)			£730,654
Key: ICER: incremental cost-effectiveness ratio; LYG, life-year gained; MET, metreleptin; SOC, standard of care; QALY, quality-adjusted life year			

Table 3: List price with [redacted] discount assuming only large vial available (BC3)

	MET	SOC	Increment
Cost of Therapy (£)	[redacted]	£48,695	[redacted]
Other Medical Costs (£)	[redacted]	£26,159	[redacted]
Total Costs (£)	[redacted]	£74,854	[redacted]
Life Years	19.18	16.23	2.95
Utility Decrements (QALYs)	-10.84	-15.65	4.82
QALYs	8.34	0.58	7.77
QALYs (undiscounted)	16.27	0.27	15.99
ICER (£)			[redacted]
Key: ICER: incremental cost-effectiveness ratio; LYG, life-year gained; MET, metreleptin; SOC, standard of care; QALY, quality-adjusted life year			

Table 4: List price with [redacted] discount on all vial sizes (BC4)

	MET	SOC	Increment
Cost of Therapy (£)	[redacted]	£48,695	[redacted]
Other Medical Costs (£)	[redacted]	£26,159	[redacted]
Total Costs (£)	[redacted]	£74,854	[redacted]
Life Years	19.18	16.23	2.95
Utility Decrements (QALYs)	-10.84	-15.65	4.82
QALYs	8.34	0.58	7.77
QALYs (undiscounted)	16.27	0.27	15.99
ICER (£)			[redacted]
Key: ICER: incremental cost-effectiveness ratio; LYG, life-year gained; MET, metreleptin; SOC, standard of care; QALY, quality-adjusted life year			

1.2 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

Incremental results included in tables 1-4 above.

Sensitivity analyses

1.3 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the highly specialised technologies evaluation. Consider using tornado diagrams.

Figures 1 and 2 present the one-way sensitivity analysis results for BC3 and 4 (i.e. with PAS applied).

Figure 1: DSA results for List price with [redacted] discount assuming only large vial available (BC3)

[redacted]

Figure 2: DSA results for List price with [redacted] discount on all vial sizes (BC4)

[redacted]

[2] For outcome-based schemes, please see section 5.8 in appendix A

1.4 Please present scenario analysis results as described for the main company/sponsor submission of evidence for the highly specialised technologies evaluation.

Tables 5 and 6 presents scenario analyses results for BC 3 and 4 (i.e. with PAS applied).

Table 5: Scenario analysis with [redacted] discount on 10mg dose (BC3)

Structural Scenario	Specific Assumptions/Inputs	ICER	QALYs Gained
Base case for decision making (BC4)	PAS price, with multiple vial sizes	[redacted]	7.77
Base case plus alternate inputs (BC4.1)	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	[redacted]	9.30
Future Price Changes: Loss of metreleptin exclusivity	Metreleptin PAS price assumed to reduce by 90% after 10 years	[redacted]	7.77
Elimination of mortality benefit of metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ damage.	[redacted]	7.77
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	[redacted]	7.54
	all organ progression probabilities decreased by 50%	[redacted]	8.05
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	[redacted]	8.02
Alternate survival extrapolation methods: GL curve parameterization	Weibull	[redacted]	8.05
	Log Normal	[redacted]	7.93
	Logit	[redacted]	7.78
Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	[redacted]	7.84
	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	[redacted]	7.59

Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	[redacted]	7.48

Table 6: Scenario analysis with [redacted] discount on all vial sizes (BC4)

Structural Scenario	Specific Assumptions/Inputs	ICER	QALYs Gained
Base case for decision making (BC4)	PAS price, with multiple vial sizes	[redacted]	7.77
Base case plus alternate inputs (BC4.1)	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension)	[redacted]	9.30
Future Price Changes: Loss of metreleptin exclusivity	Metreleptin PAS price assumed to reduce by 90% after 10 years	[redacted]	7.77
Elimination of mortality benefit of metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ damage.	[redacted]	7.77
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	[redacted]	7.54
	all organ progression probabilities decreased by 50%	[redacted]	8.05
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	[redacted]	8.02
Alternate survival extrapolation methods: GL curve parameterization	Weibull	[redacted]	8.05
	Log Normal	[redacted]	7.93
	Logit	[redacted]	7.78
Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	[redacted]	7.84
	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	[redacted]	7.59

Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	[redacted]	7.48

Miscellaneous results

The results of the preliminary analysis of early initiation are not described elsewhere and are shown on in the table below.

Table 7: Early treatment initiation at age 1 results (CGL**)**

Structural Scenario	**Specific Change**	**ICER**	**QALYs Gained**
Early treatment initiation at age 1: CGL	PAS price, multiple vial sizes	[redacted]	12.35
	PAS price, multiple vial sizes plus double hyperphagia decrement, plus parental disutility of -0.05 per period	[redacted]	14.51

1.5 Please present any probabilistic sensitivity analysis results and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis results have been presented for the final decision making base case (BC4), with the scatter plot in figure 3, and the CEAC in figure 4.

Figure 3: Scatter plot with PSA results for List price with [redacted] discount on all vial sizes (BC4)

[redacted]

Figure 4: Cost-effectiveness acceptability curve [redacted] discount, all vial sizes) (BC4)

1.6 If any of the criteria on which the Patient Access Scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.

N/A

Impact of Patient Access Scheme on ICERs

1.7 For financially based schemes, please present the results of the value for money analyses showing the impact of the Patient Access Scheme on the base-case and any scenario analyses. If you are submitting the Patient Access Scheme at the end of the evaluation process, you must include the scenario with the assumptions that the HST Evaluation Committee considered to be most plausible.

Table 7 presents a summary of the base case results at metreleptin list price and with PAS for all patients expected to be covered by the licensed indication. A key scenario analysis (BC4.1) has been presented with PAS applied to indicate the potential quantifiable ICER based on plausible assumptions. The estimated drug budget impact implications have also been presented in Table 7.

Table 8: Summary of list price and with PAS ICERs

	ICER	QALYs Gained	5 year cumulative budget impact
Base case, list price, single vial size (BC1)	£1,432,391	7.77	£133,045,965
Base case, list price, multiple vial sizes (BC2)	£730,654		£67,802,818
Base case, PAS price, single vial size (BC3)	[redacted]		[redacted]
Base case, PAS price, multiple vial sizes (BC4)	[redacted]		[redacted]
PAS price, multiple vial sizes, adjusted utility values (larger decrement for hyperphagia, allowance for improvement in heart abnormality) (BC4.1)	[redacted]	9.30	Same as BC4
Key: BC, base case; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year			

In conclusion, Aegerion have set a simple PAS price discount in order to deliver an ICER for metreleptin (as per BC4 and 4.1 in table 7 above) that can be considered a cost-effective use of NHS resources, once account is also taken of the unquantified QALY and wider societal and non-health benefits that could be attained for patients and their family/carers.

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Highly Specialised Technology Evaluation

Metreleptin for treating lipodystrophy ID861

Dear Neale,

The Evidence Review Group, Kleijnen Reviews Ltd., and the technical team at NICE have looked at the submission received on 22 January 2018 by Aegerion In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to some of the data (see questions listed at the end of the letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide a written response to the clarification questions by **12noon** on **27 February 2018**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) in your response as this may result in your information being displaced or unreadable.

If you have any further queries on the technical issues raised in this letter then please contact Orsolya Balogh, Technical Lead (Orsolya.balogh@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (Joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director – Highly Specialised Technologies
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Literature searching

A1. Please provide a full version of the Cochrane Library search given in Appendix 17.1.4 (pg 223 of the CS), lines #10-#12 appear to be incorrectly displayed.

A2. Please provide a copy of the search strategy for Econlit, it appears to be missing from Appendix 17.3.4 but is reported as being searched in section 17.3.1.

A3. Please provide full details of how un-published data were sought, e.g. were patient organisations and treatment centres, such as Addenbrookes hospital, contacted? The PRISMA flow chart for the SLR (figure C14 in the CS, page 71) reports the inclusion of 29 publications from records identified from electronic searches, but only 25 publications are listed. Please can you confirm whether the total of 29 publications was intended to include the un-published CSRs and related trial registry entries. In addition, please provide a list of all 29 included publications and list for each publication how they were used in the submission/model.

A4. Please provide full details of any search strategies used to identify comparator and/or natural history studies.

A5. Please explain why HIV-associated LD was considered as an exclusion criterion in the searches in the clinical effectiveness (e.g. Table C11) whereas in the cost-effectiveness, studies focusing on HIV-associated LD were selected for data extraction.

A6. **Priority Question**: Please provide copies of all tables, figures and graphs referred to, but not included in the text of the CSRs:
a) NIH 991265/20010769 (NCT00025883). Open-label, single-arm study conducted at the NIH in the US.
b) FHA101 (NCT00677313). Open-label expanded access study designed to provide metreleptin under a treatment IND protocol for the treatment of patients with diabetes mellitus and/or hypertriglyceridaemia associated with LD.

A7. Priority Question: Please provide detailed explanation/justification why data reported in the clinical effectiveness section of the CS were not used to inform cost-effectiveness analysis and, conversely, why the clinical effectiveness evidence used in the cost-effectiveness analysis is not reported in the clinical effectiveness section of the CS. The cost-effectiveness analysis appears to be based on two studies (NIH Follow-Up study and GL/PL Natural History study) which are not included in the clinical effectiveness section of the CS. Similarly, the reported methods for the cost-effectiveness analysis do not describe whether/how the data described on the clinical effectiveness section (e.g. changes in HbA1c and changes in triglycerides) were used to inform the cost-effectiveness analysis.

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A8. Please also explain how the GL/PL Natural History study, used to provide control group data for the cost-effectiveness analysis, was selected. Was a literature review conducted? If yes, please provide a full search strategy with results. Also, please state if there were other sources that could have been used and, if so, on what basis was this study preferred?

A9. **Priority Question**: Please provide copies of any reports or other data sources relating to the ongoing studies, referred to in section 4.1 of the CS which were used as the source of clinical evidence for cost-effectiveness analysis:

- NIH Follow-Up study
- GL/PL Natural History study

A10. Priority Question: Table A1 under the heading 'Rationale for variation from scope' indicates that the relevant PL population is those within the following age group: adults and children 12 years of age. However, Tables C16 and C17 (CS, pages 83 and 84) defined the PL subgroup as 'patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L' and 'patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L,' respectively i.e. there is no mention of an age related subgroup.
For studies NIH 991265/20010769 and FH101 please provide subgroup data to match the expected licensed indication, as described in table A1 (CS, page 19) under the heading 'Rational for variation from scope.' Please also provide these data for the studies used to inform the cost-effectiveness analysis (NIH Follow-Up study and GL/PL Natural History study).

A11. Priority Question: The scope defines the comparator as 'established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes)'. Please explain how studies for this comparator were sought and selected and provide full results. If data for any other comparator are available then please also provide a comparison with the results from the metreleptin studies, using either a naïve comparison or an adjusted comparison.

A12. The clinical effectiveness section of the CS includes no data or only very limited data for the effectiveness regarding a number of the clinical outcomes specified in the scope.
No data: liver cirrhosis; complications of diabetes; organ damage (including heart and kidneys); mortality (other than as an AE); pancreatitis (other than as an AE) effects on appearance.
Partial/very limited data: use of drugs other than diabetes therapies; growth and development; reproductive dysfunction; infection. Please confirm that no additional data are available for these outcomes, either from the NIH follow-up study, from publications related to NIH 991265/20010769 (NCT00025883) or FHA101 (NCT00677313), from the EAP, or from any other study/source of which you are aware. If data is available, please provide this in your response.

A13. Priority Question: The section of the CS dealing with safety and adverse events includes the following text:
'Across the 148 patients included in LD studies, 6 (4%) patients (4 with GL and 2 with PL), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and

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hypertriglyceridaemia. One of the patients who developed septic shock concurrent with pancreatitis died; the other 5 patients recovered and continued on treatment. Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridaemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridaemia.'
Given the reported non-compliance rates of between 9 and 19%, please explain/justify why the increased risk of pancreatitis on discontinuation of therapy is not considered in the cost-effectiveness analysis.

A14. Please confirm that no data are available about the incidence of pancreatitis in patients who remain on treatment, i.e. does continuous treatment reduce the risk of pancreatitis?

A15. The CS reports some limited data, from the NIH 991265/20010769 (NCT00025883) study population, on hyperphagia (section 9.6.1.4.4 of the CS) and on liver pathology (section 9.6.1.4.3 of the CS). These outcomes are not listed in the protocol for NIH 991265/20010769 (NCT00025883) and appear to be derived from separate 'mini studies' conducted by investigators. Please clarify.

A16. Section 6.2 (CS, page42) states: 'There is limited published data available on the incidence and prevalence of LD in England. One study (Chiquette et al. 2017) identified in the literature search was considered but was not deemed accurate or generalisable for a UK population and the anticipated metreleptin licence. More relevant and accurate estimates are available based on EAP data from a decade of metreleptin use in UK clinical practice at Addenbrooke's.' The ERG has noted that Chiquette et al. 2017 reported the range of worldwide prevalence of all LD to be 1.3–4.7 cases/million, with 4.7 cases/million in the UK. Using figures from Addenbrooke's and population of England (26 in 55 million) equates to 0.47 per million. The ERG notes this is a substantial 10-fold difference in the estimates derived from these two sources. Please justify why the estimates from Chiquette are not considered to be relevant and why the data from Addenbrook's is preferred.

A17. Please explain why Japanese patients are not relevant to this submission (CS, page 73)?

A18. For Table C13 (CS, page 73), please provide a reason why each study was excluded.

A19. Please provide a) the number of UK patients in each of the included studies, b) how long each of the UK patients have received metreleptin, and c) how long they have been followed up. Please provide these data both for the studies included in the clinical effectiveness section of the CS [NIH 991265/20010769 (NCT00025883) and FHA101 (NCT00677313)], and for the studies used to inform the cost-effectiveness analysis (NIH Follow-Up study and GL/PL Natural History study).

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A20. Please provide a reason why 8 GL patients were transferred to another program (e.g. lack of effect, AEs), noted in Table C18 (CS, page 87).

Section B: Clarification on cost-effectiveness data

Disease Progression

B1. **Priority Question:** In the model, most of the simulation calculations are based on the data in the "*RWD_**" sheets but the data in these sheets are not clear.

Please explain how the RWD data provided in the cost-effectiveness model were generated and what each entry in the "*RWD_**" sheets means. For instance:

- What is difference between the data in "*RWD_HeartAbnormal _hypertension*" and the data in the "*RWD_HeartAbnormal _nonhyper*" sheets? Additionally, please clarify how they are combined in the "*RWD_HeartAbnormal*" sheet. The ERG note that it appears to be based on a control on the "*enable alternate scenario*", in cell "*B9*" from "*Background Lookups and Calcs*" sheet, but could not identify the original checkbox.
- In some patients, the number of organ abnormalities decreased in time, for instance, for patient 1, liver, kidney and pancreas abnormalities present at baseline seems to be resolved after the first year. Please explain the reasons of these type of organ impairment improvements, as they were not considered in modelling of the organ abnormality progression, explained in Section 17.6 (total number of organs assumed to stay the same or increase in time).
- Data in the "*RWD_Hypoevents*": please confirm if this relates to the total number of hypoglycaemia events patient experienced in that year.
- Data in the "*RWD_Attributes*" sheet: two measurements for each attribute (hyperphagia, ability to work, etc.) For each attribute, the values under "0" column are used for the SoC arm patients and the values under the "1" column are used for metreleptin arm patients. It is stated in the company submission that the values under the "1" column indicate the improvement from the baseline, however the details on the size/characteristics of these improvements are not provided. Please provide more detailed information on these attributes. What does "0" and "1" as attribute values mean exactly? What does the composite improvement indicator mean and when/how it is measured? Why were the improvements in these attributes not presented in the clinical effectiveness part of the submission?
- Data in the "*RWD_Discontinuation*" sheet: Please explain the figures in this sheet. Please explain whether 0 means that the patient discontinued? What does a value between 0 and 1 mean (like 0.11 in cell *X22*). Does it mean that the patient continued the medication 11% of time? Why is the 1st year discontinuation not included in calculations? Please explain the calculations that yielded 2.045% as the overall discontinuation rate and explain what the main reasons for the discontinuation were (e.g. lack of efficacy, neutralizing antibodies, side effects).
- Data in the "*RWD_Leptin*" sheet: please explain why only baseline values are provided?

B2. **Priority Question:** The RWD data presented in "*RWD_**" sheets are used in the calculations given in the "*SIM_**" sheets, while simulating the disease progression. However,

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calculations in these sheets are not clear. Please explain the calculations in the "*SIM_**" sheets, for instance:

- Please explain, step by step and cell by cell, how the probabilities of 0, 1, 2, 3 and 4 organ abnormalities and the average number of abnormalities were calculated both for metreleptin and SoC patients and the reason of using "buffer" calculation sheets (e.g. *SIM_NumOrgansAbnormal* and *SIM_NumOrgansAbnormal_Buffer* sheets) and sheet for flagging issues ("*SIM_Flag*").
- "*SIM_hypoevents*" sheet does not include any calculation, but includes only hardcoded data. Please explain what these data mean (indicating a source/assumption) and provide the calculations for the hypoglycaemic event extrapolations. Also please explain what assumptions were taken for the hypoglycaemic events under SoC.
- Please explain the simulation of the discontinuation as well as its implications in terms of cost, utility and transition probabilities.
- In the simulation sheets for attributes other than organ impairment and blood glucose and triglyceride levels (e.g. "*SIM_ParentalDisutility, SIM_ProgressionSpeed, SIM_Hyperphagia, SIM_Reprod1, SIM_Physapp"* and "*SIM_AbilityWork"*), the corresponding data from the NIH follow-up study are used (can be seen in the "*RWD_*"* sheets). It seems that when the RWD data are missing, it is automatically assumed "0" in the simulation. Please clarify if this was a programming error or a deliberate assumption.

B3. **Priority Question:** Please provide additional description of the methodology in deriving the transition probabilities and further justification for some of the assumptions around progression of organ abnormalities. For example:

- Please clarify why the type of affected organ (pancreas, kidney, heart and liver) and the severity of an organ abnormality (e.g. ectopic fat deposit on an organ or an organ failure) were not taken into consideration in the analysis. Based on this assumption in the CS, the cost and health outcomes from an ectopic fat deposit around the liver are the same as those from a myocardial infarction or from a kidney failure. In addition, this level of abnormality accumulation overlooks the possibility of having more than one abnormality on the same organ (e.g. fat deposit on liver in addition to cirrhosis). Please provide the detailed patient level data from both the NIH follow-up trial and GL/PL natural history study, where the type of the afflicted organ as well as the type/severity of each observed organ impairment can be traced.
- On page 259 of the CS, above Table 71, it is explained that while the patients from the GL/PL natural history study have data from birth, for patients in the NIH follow-up study, data are only available since the start of their treatment. The submission also notes that the resulting truncated data may lead to biased estimates. Please explain the size and the direction of this bias and please justify why no attempt was made to correct for this bias?
- Please explain how to interpret the steep decline in the KM curves near t=0 in all sub-figures depicted in Figure 35, page 257 of the CS. It suggests that once a patient is being observed, 20% of patients immediately develop an organ failure, regardless of how many organs were already damaged.

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- Please justify the plausibility of the assumptions below by conducting formal statistical tests (e.g. t test, F test, etc.) on the available patient level data (eligible patients from the NIH follow-up trial and GL/PL natural history study):
    - the probability distribution for the total number of impaired organs would follow Markov memoryless property (e.g. transition from one state to another does not depend on the time spent in the former state)
    - probability of developing two or more organ abnormalities in a year or improvement of the existing organ abnormalities would be always zero
    - the patient characteristics such as age, gender, type of lipodystrophy, type of organ damage and severity of the abnormality, time on metreleptin treatment, blood triglyceride levels have no impact on the transition probabilities for the number of impaired organs.
- If possible, please provide a de-novo statistical analysis for the estimation and the extrapolation of organ abnormality progression, using common, published methods for transition probability estimation (e.g. multi-state models or maximum likelihood estimates: https://www.ncbi.nlm.nih.gov/pubmed/11788980 https://cran.r-project.org/web/packages/msm/vignettes/msm-manual.pdf), using the pooled dataset (including label-eligible patients from both NIH follow-up study as well as the natural history study) [e.g. multi-state models or maximum likelihood (The statistical analysis should include all relevant covariates , where the relevance of the covariates can be determined based on properly conducted formal statistical tests, as required in the previous bullet point. Please implement the disease progression probabilities derived from this de-novo statistical analysis to the model.

B4:

a) Please provide scenarios, in which the attributes like hyperphagia, ability to work, reproduction, physical appearance and fast disease progression do not stay at their baseline values but may change over time.

b) In the CS, neuropathy, amputation and retinopathy were named in the list of attributes used in the electronic model, which characterised an individual patient's health (first paragraph of section 12.1.6 of the submission). However, in the electronic model, the ERG were unable to find these attributes. Please confirm that these attributes were not actually included in the model as separate attributes and explain the reason for that.

c) Please indicate how "ability to work" was operationalised in the model. For example, explain whether the probability of being partially employed and unemployed, as well as being retired, were taken into consideration.

B5. Please explain the improved attribute values used for metreleptin (hyperphagia, ability to work, reproduction, physical appearance and fast disease progression) in detail and provide scenarios where the baseline and follow-up attribute values are the same in both metreleptin and SoC arms.

B6. The "Progression Speed" attribute has an impact on QoL and cost calculations but it has no influence on the disease progression probabilities in the model. Could you please explain how progression speed is measured and the rationale for its impact on QoL and cost calculations without having any impact on disease progression probabilities? If this attribute

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is related to the speed of disease progression, then please incorporate a scenario where the disease progression probabilities are also affected by this attribute.

B7. **Priority Question:** Please justify why only a "last observed carried forward" approach was followed in the extrapolation of glucose and triglyceride levels. Please explore other methods for blood glucose (e.g. regression imputation or assuming a linear increase in HbA1c as in other type-2 diabetes models (http://www.core-diabetes.com/)) and triglyceride (e.g. mean imputation) extrapolation. Also, please present a comparison of these attribute values used in the economic model with the values presented in the clinical effectiveness section.

Survival analysis

B8. **Priority Question:** In the company's model, the 'percentage of people alive' at the end of the time horizon is considerably higher than zero (e.g. average probability of being alive at the end of the time horizon is 26.7% in the metreleptin arm). Please provide a scenario with a long time horizon, where the average percentage of people being alive at the end is almost zero. Note that it might require some reprogramming of the model, so that it accommodates longer time horizons than 60 years (maximum).

B9. **Priority Question:** The ERG considers that some of the survival estimates in the submission may lack face validity. For instance, in the model, PL patients who have a lower number of impaired organs compared to the baseline average of the NIH follow-up study, have a better life expectancy than the UK general population.

- Please confirm that mortality estimates for PL/GL patients should not be below the national lifetable age/sex specific values. Please provide alternate clinically plausible mortality estimates (which cannot be lower than the UK general mortality figures, even if the patient has no organ abnormality). Please implement these estimates in the model.
- For the mortality of GL patients, data from the NIH follow-up was used (CS page 259). For the extrapolation of that data the approach as outlined by Latimer was followed, but it appears that a crucial step was not included, i.e. checking the clinical plausibility of the extrapolated part of the curve. Hence, please provide external data or expert opinion to assess if another parametric function than the exponential should be used in the base case.

B10: **Priority Question:** Please answer the queries related to the survival analyses below:

- The survival study explained in Appendix 6 includes an extrapolation exercise (17.6.2.2) for the survival of the GL/PL patients using parametric models and national life tables, followed by an estimation exercise (17.6.2.3) for the relationship between organ abnormality and mortality. While the extrapolation exercise was conducted on the patients from the NIH follow-up study, the estimation exercise was conducted on the patients from the GL/PL natural history study. The hazard ratio coefficient from the estimation exercise is applied to the parametric/life table survival curves obtained from the extrapolation exercise. Please explain why the natural history dataset is used for the estimation exercise instead of NIH follow-up dataset. Also provide de-novo extrapolation and estimation exercises, using data from a pooled dataset including label-eligible patients from both NIH follow-up and natural history studies,

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incorporating the study ID as a separate covariate. Please implement the findings of this de-novo analysis to the model.

- The results in Table 75 (page 266) suggests that the number of impaired organs is a significant covariate, but the ERG question if it is the only one, noting that p-values alone might not be the only decision criteria to decide on which covariates to include. Please provide all relevant details (dataset used, statistical codes compiled as well as the whole statistical outputs from the analyses including R^2 and goodness of fit results) for the survival analysis exercises conducted (base case and those in Table 75) with their explanations and provide other prognostic survival models with additional covariates (for example type of the disease, treatment received and any other relevant covariates), on the natural history dataset, NIH follow-up study dataset and the pooled dataset, including only label-eligible patients.
- In the model, it is not clear why the UK life table is referred to in the end of each formula in the "*SIM_Alive*" sheet (from column M and onwards). Please explain.
- Please explain why the age of the patient is taken as an index for the PL patients survival calculations, whereas for GL patients, this index is the time from the start of the treatment?

Matching:

B11**. Priority Question:** Please provide all further details (datasets used, statistical codes compiled as well as the outputs of the statistical analysis) of the matching exercise in 17.6.2.4 with their explanations. Please confirm whether these analyses are in line with the NICE DSU TSD 17. Please explain why only age, gender and initial organ damage used in the matching. Please also explain why the matched SoC transition probabilities in Table 78 suggest a faster progression compared to the unmatched SoC transition probabilities in Table 70.

B12. It is not clear how the KM plots for SoC were generated in Figure 43 (page 274). No survival analysis results for the patients under SoC were presented in the clinical effectiveness part of the submission (e.g. 6.1.3). Please provide the survival data used and the corresponding KM curves from the natural history PL/GL patients.

Utilities:

B13: **Priority Question:**

a) Please provide a detailed explanation for why DCE was chosen as a method to estimate health state utilities, after EQ-5D was deemed to be insufficient.
b) Please provide more detailed information regarding the DCE that was done to find disutility estimates pertaining to lipodystrophy disease attributes. This information should provide details regarding the experimental design, explaining for example whether an orthogonal design, a full factorial design or some other experimental design was used.
c) Please also explain the selection process of attributes, given that several of them may be correlated.
d) Please, also include all details of the statistical models (datasets used, statistical codes compiled as well as the outputs of the statistical analysis) that have been explored in 17.5.2.5, in order to estimate the utility values, incorporating the detailed output of the analyses.

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B14: **Priority Question:** The ERG notes that additive approach followed in the submission of applying attribute disutilities in QALY derivation often leads to negative values for total QALYs (see for example the number of QALYs for SoC in Table D49). This would imply that *on average*, patients receiving SoC would rather be dead than living with lipodystrophy. Also, one of the two references in the CS, Ara and Brazier 2012 suggests using the multiplicative approach together with a range of sensitivity analyses. Note that the other reference, Viney et al. 2014, also shows preference for a model with interaction (possibly multiplicative) rather than additive because "*interaction terms reflect their preference complementarity, namely, that two or more health problems' combined impact is less than the sum of the individual main effects*". This seems reasonable in this setting when multiple attributes define the health status of a patient.

- Please adapt the analysis in 17.5.2.5 to provide disutility estimates that are fit for use in the multiplicative approach.
- Please modify the model such that it accommodates the application of the disutilities in a multiplicative way as an option and present an analysis using the estimates requested in the previous bullet point .

B15: Figure 33 (page 240) of the CS shows a comparison of the utility decrements obtained by the DCE with some values obtained from the literature.

- Some important utilities e.g. hypoglycemia, for which there is rich literature available have not been included. Please provide a comparison between DCE and literature-based utility decrements for all the utility decrements included in the model. When such a comparison is not possible please provide some discussion on the validity of the obtained utilities.
- The purpose of this validation exercise is not clear. Differences between DCE and published values appear to be large in some cases, but no consequences are discussed in the CS. Please explain what criteria are applied to assess the face validity of the disutility values of the DCE, and what should be done if the DCE values lack face validity.

Costs

B16: **Priority question:** The primary analysis is based on the availability of multiple vial sizes (i.e., 11.3, 5.8, and 3 mg vial sizes). However, only the 11.3 mg vial is currently available. An anticipated availability of 3 months for the smaller vial sizes is described in the submission. Please confirm the certainty of this anticipated availability.

B17: The calculation of the weighted average price of metreleptin is unclear (in sheet *"Drug Costs"*), especially the column *"assumed Cambridge average dose following titration (TBC)"*. Please provide details of the dose estimations and the calculation of the weighted average price of metreleptin.

B18: Drug administration costs such as home delivery and self-administration training are not separately included in the model as these activities will be funded by the company at no additional cost to patients or NHS. Please confirm that the company will also fund these costs in the future.

B19: "Additional resource use costs, such as laboratory tests and office visits, are difficult to quantify given the heterogeneity of disease characteristics and lack of quality data. In this model, the resource use costs are assumed to occur equally to both metreleptin treated and

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standard of care patients". Please justify the plausibility of this assumption from clinical trials, literature and/or experts' opinion.

B20: Costs of standard of care are estimated at £3,000. Please explain how these costs of standard of care are estimated, and please separate all costs into resource use in natural units and unit cost.

B21: According to the CS, costs per patient with an abnormality are estimated with the following formula: *(Number of lipodystrophy-related inpatient stays per annum per patient/ Fraction of patients with an abnormality) * Cost per inpatient stay*. However, in the model, it seems like costs per patient with an abnormality are estimated differently to this formula. Please explain how costs per patient with an abnormality are estimated in the model and whether this is consistent with the formula in the CS.

B22: In the base-case analysis, no costs are associated with hyperphagia, PCOS, inability to perform school or work, impaired physical appearance, or abnormal laboratory levels, since the costs of these attributes likely vary substantially and are hard to quantify. Please justify the plausibility of this assumption from clinical trials, literature and/or experts' opinion. Please explain why no assumptions based on literature were made to estimate these costs. Subsequently, the submission states: "As these attributes are more likely to be present in patients who do not receive metreleptin, including £0 in associated costs is conservative". Please provide any evidence for this statement (i.e. that these attributes are more likely to be present in patients who do not receive metreleptin).

B23: Please provide all details of the estimation of the costs per patient with abnormality (Table D40). Please explain why no additional costs were associated with triglyceride and glucose control and badly controlled triglyceride and glucose levels.

B24: The model base case does not include costs to caregivers (formal care through the NHS), costs associated with routine monitoring, and drug administration costs such as home delivery and self-administration training (see 12.3.9). Please justify the plausibility of this assumption from clinical trial, literature and experts' opinion.

B25: In the model, it seems that a proportion/weight is applied to the cumulative number of organ abnormalities to calculate the probability of a specific organ abnormality. However, it is not clear how these proportions/weights (e.g. Kidney, Liver, Heart, and Pancreas) among all organ abnormalities were derived. Also, the application of these weights seems to differ between cost and utility calculations in the model (in "*COS_Organ*" and "*TDU_Organ*" sheets). Please explain how these weights are derived, how they are apply to the cumulative number of organ abnormalities in cost and utility calculations and explain the differences in the cost and utility calculations.

B26: **Priority Question:** Resource use is identified by two clinical advisors who treat lipodystrophy at Addenbrooke's Hospital. Please provide more details of the communication between the company and the clinical experts for all KOL based assumptions. Please include the anonymised information about the clinical experts, , the list of expert recommendations and justifications for clinical assumptions used in the model (e.g. the assumed Cambridge average dose of metreleptin), questionnaires completed by the clinical advisors, etc and if possible please also provide minutes of any meetings.

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Adverse events

B27: Explain why no adverse events other than hypoglycaemia were incorporated in the model (e.g. neutralizing antibodies, fatigue, injection site issues, decreased weight, impact of pancreatitis following discontinuation etc.). Please include all clinically relevant adverse events in the economic model. Discuss any implications of excluding adverse events in the economic analyses.

Budget impact analysis

B28: The eligibility for lipodystrophy (13.1) and the uptake rate of metreleptin (13.2) are based on expert clinical opinion. Please provide all details of the data used for these assumptions and provide the budget impact calculations within the model.

Validation

B29: **Priority Question:** Please provide all the details of the validation exercise mentioned in Section 12.7 of the CS. Did the validation exercise include all the steps (internal validation, cross-validation, etc…) as explained for example in the AdvisHE (https://advishe.wordpress.com/) tool? If not, please include these steps as well.

Sensitivity/scenario/subgroup analyses

B30: **Priority Question:** The ERG has identified a number of issues/discrepancies related to the sensitivity/scenario analyses

- Please provide the criteria for the parameters to be included into PSA and DSA. Parameters such as the time horizon, and discount factor should not be included in the sensitivity analyses, as their uncertainty can be characterised under methodological uncertainty and therefore should be explored in scenario analysis. Metreleptin price/costs should not be explored in sensitivity analyses, as well. If there are factors that impact annual metreleptin acquisition costs (such as patient weight), they should be varied independently from metreleptin price.
- It is not clear how the upper and lower limits for the parameters included in the DSA were obtained, as these are not the upper and lower 95% CI limits. Please explain where these originate from.
- It seems that the standard deviation was used for each parameter (instead of standard error), and some of the standard deviation estimates are implausible in Table D43 (i.e. negative). Furthermore, their source references are unclear. Also, for some of the parameters, the probability distribution chosen seem to be incorrect (e.g. normal distribution for disease progression or discontinuation rates, which might lead to negative estimates). Please explain where the uncertainty estimates are generated from for each parameter, and the rationale behind the choice of the distributions.
- Please provide more details about how the PSA is conducted: inner and outer loop sizes, how patients are selected (with/without replacement), whether the patients are the same in the two arms, etc. Please confirm whether DSU guidelines (TSD 15) for conducting PSA in a patient-level model were followed or not. Also please provide

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the average and 95% CI of the PSA results for total/incremental costs, total/incremental QALYs for the base case and all subgroup analyses.

- Please explain the rational of the multi-way scenario analysis assumptions, why it was presented as base case 4.1 in the executive summary, and the details of the changes (e.g. further justification for the resolution of heart abnormalities)
- Please provide guidance explaining how to implement each of the scenarios in Table D51 in the model (which cells need to be changed, which controls should be activated, etc.)
- Please provide new PSA and DSA results with an appropriate list of parameters, having appropriate upper and lower limits, appropriate PSA methodology, mean and standard error values and probability distributions.
- It seems like in the subgroup analyses, for each subgroup, the average results of the patients that fall into the corresponding subgroup are calculated. This approach assumes that there is no difference in terms of transition probabilities (for disease progression or survival), health care resource utilisation and utilities among all subgroups. Please justify if this assumption is plausible from the patient level data from the NIH follow-up and GL/PL natural history studies, otherwise incorporate the subgroup specific inputs in the model.

Impact beyond direct health benefits

B31: In the CS, in section 14.1, it is mentioned that after metreleptin initiation, the percentage of not working or part-time working caregivers was decreased around 80% (From 35% at the baseline to 7% after follow-up). Please clarify when the latter figure (7%) was measured. Please clarify if this decrease is attributable to the treatment or the fact that the patients grow up.

B32: In the CS, in section 14.3, type 2 diabetes (T2DM) indirect costs for UK were provided as a proxy. Please justify why indirect costs for T2DM would be a proxy for the indirect costs for LD. Also, please provide more details and the source of the hospitalisation figures (20% of LD are hospitalized at least once a year, with some hospitalised more than 5 times a year).

B33: Please provide estimates for the indirect health care costs due to additional years after receiving metreleptin.

Section C: Textual clarifications and additional points

C1. Section 12.2.4 of the CS includes the following text:
'Hypoglycaemia was included in the cost-effectiveness analysis as an adverse event. Only treated patients were eligible to experience hypoglycemia and during the NIH study data period, a count of observed hyperglycemia events was assigned to each patient. After the end of observation, an annualized count of hyperglycemia events was assigned to remaining model periods.'
Please confirm that the above text should refer to hypoglycaemia and not hyperglycemia throughout.

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C2. Table C20 'Critical appraisal of study NIH 991265/20010769' is incomplete. Please provide the missing content for the following two items:
'Was the follow-up of patients complete?'
'How precise (for example, in terms of confidence interval and p values) are the results?'

C3. Table C15 (CS, page 78) is headed 'Summary methodology for study FHA101', but appears to contain both a repeat of information for study NIH 991265/20010769 and information for study FH101. Please provide a corrected version of this table.

C4. There appears to be a transcription error regarding the BC2 definition – between main submission (page 15) and PAS submission. Please correct the text appropriately.

Metreleptin for treating lipodystrophy ID861 - Response to clarification questions 13th February 2018

Submitted by Aegerion Pharmaceuticals Ltd.

Highly Specialised Technology Evaluation (HST)
National Institute of Health and Care Excellence

Submitted 27th February 2018

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List of Abbreviations

AGL	Acquired generalised lipodystrophy
ALT	Alanine aminotransferase
APL	Acquired partial lipodystrophy
AST	Aspartate aminotransferase
BSCL	Berardinelli-Seip congenital lipodystrophy
CE	Cost-effectiveness
CFAS	Controlled Concomitant Medication Full Analysis Set
CI	Confidence interval
CGL	Congenital generalised lipodystrophy
CSR	Clinical study report
CUH	Cambridge University Hospitals
DCE	Discrete choice experiment
DSA	Deterministic sensitivity analysis
EAP	Early Access Programme
EMR	Electronic medical records
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPL	Familial partial lipodystrophy
FPLD	Familial partial lipodystrophy, Dunnigan variety/ familial partial lipodystrophy type
GL	Generalised lipodystrophy
GPRD	General Practice Research Database
HbA1c	Glycated haemoglobin
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HST	Highly specialised technology evaluation
HSUV	Health state utility values
HTA	Health technology assessment
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICER	Incremental cost-effectiveness ratio
ISM	Individual sampling modelling
IV	Intravenous
KM	Kaplan-Meier
LD	Lipodystrophy

LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
MA	Marketing authorisation
MAE	Mean absolute error
MET	Metreleptin
MH	Moderate hypoleptinaemia
MID	Minimum important difference
MMRM	Mixed-effect Model Repeated Measures
MRI	Magnetic resonance imaging
MSM	Multi-state model
NIH	National Institutes of Health
NHS	National Health Service
NASH	Non-alcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
PCOS	Polycystic ovary syndrome
PL	Partial lipodystrophy
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RMSE	Root mean square error
RWD	Real-world data
SD	Standard deviation
SH	Severe hypoleptinaemia
SLR	Systematic literature review
SMD	Standardised mean differences
SOC	Standard of care
T2DM	Type 2 diabetes mellitus
TG	triglycerides
TTO	Time trade-off
UK	United Kingdom
US	United States
UTSW	University of Texas Southwestern

1. Overview

This document contains Aegerion's response to clarification questions from the Evidence Review Group, Kleijnen Reviews Ltd.(ERG), and the technical team at NICE that were sent to Aegerion on Tuesday 13th February 2018. We have attempted to address all questions as fully as possible within the timeframe permitted (deadline of 27th February 2018). However as agreed with NICE and the ERG on the teleconference 21st February 2018, model adaptations and some supplemental analyses supporting questions B4, B7, B8, B14, and B29 have been given an extended response submission date of 2nd March 2018 and will follow in a separate submission.

2. Response to clarification questions

Please find below responses by Aegerion to each of the questions raised by the ERG, Kleijnen Reviews Ltd, and the technical team at NICE.

Section A: Clarification on effectiveness data

Literature searching

A1. Please provide a full version of the Cochrane Library search given in Appendix 17.1.4 (pg 223 of the CS), lines #10-#12 appear to be incorrectly displayed.

Response: Please see the full version of the Cochrane Library search.

Search Name: The Cochrane Library
Date Run: 12/03/17
Description:

ID	Search Hits
#1	MeSH descriptor: [Lipodystrophy] explode all trees 180
#2	Lipodystrophy:ti,ab,kw (Word variations have been searched) 285
#3	MeSH descriptor: [Endocrine System Diseases] explode all trees 28665
#4	MeSH descriptor: [Lipid Metabolism Disorders] explode all trees 5887
#5	MeSH descriptor: [Skin Diseases, Metabolic] explode all trees 185
#6	MeSH descriptor: [Metabolic Diseases] explode all trees 32683
#7	MeSH descriptor: [Nutritional and Metabolic Diseases] explode all trees 42727
#8	(metreleptin or myalept or leptin):ti,ab,kw (Word variations have been searched) 2001
#9	MeSH descriptor: [Leptin] explode all trees 876
#10	{or #1-#7} 53101
#11	{or #8-#9} 2001
#12	{and #10-#11} 753

(Cochrane Database of Systematic Reviews: Issue 2 of 12, February 2017: 0
Database of Abstracts of Reviews of Effect (DARE): Issue 2 of 4: 3
Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2017: 749

Health Technology Assessment Database (HTA): Issue 4 of 4: 1)

A2. Please provide a copy of the search strategy for Econlit, it appears to be missing from Appendix 17.3.4 but is reported as being searched in section 17.3.1.

Response: This was an error and the EconLit database was not searched**.**

A3. Please provide full details of how un-published data were sought, e.g. were patient organisations and treatment centres, such as Addenbrookes hospital, contacted? The PRISMA flow chart for the SLR (figure C14 in the CS, page 71) reports the inclusion of 29 publications from records identified from electronic searches, but only 25 publications are listed. Please can you confirm whether the total of 29 publications was intended to include the un-published CSRs and related trial registry entries. In addition, please provide a list of all 29 included publications and list for each publication how they were used in the submission/model.

Response: A list of all the 29 publications identified in the clinical SLR, together with reasons for their inclusion or exclusion in the submission, is shown below in Table 1 - they were all published studies. Overall 16 published studies relating to study NIH 991265/20010769 were identified in the SLR (please note there was an error in Section 9.3.1 Table C12 in the submission, which only cited 15 studies - the study by Chong 2009 had been accidently omitted). However, the integrated CSR for study NIH 991265/20010769 provided by Aegerion was considered more robust than these individual studies (which only reported on subsets of patients from the integrated CSR). The CSR wasn't included as one of the 29 studies in the PRISMA diagram but was used in lieu of the publications identified. The same was true for study FHA101, where one publication was identified, however data from the CSR, which included more patients than the publication, were presented instead (but not included separately in the PRISMA).

A further 9 publications regarding clinical studies of metreleptin were identified in the SLR but were excluded from the submission for reasons detailed in Table 1 (and please see the answer to question A18). These studies are as listed in Table C13, Section 9.3.2 of the submission.

Other studies which were not listed in Section 9.3.2 (they were included in the text in Section 9.2.2) were:

- Two publications from the same group that reported the results of a SLR and meta-analysis into the effects of metreleptin on metabolic and hepatic endpoints in patients with LD syndromes not associated with the use of HIV protease inhibitors;
- One comparator study to evaluate the effect of diet intervention and oral zinc supplementation on the metabolic control of CGL (also known as Berardinelli-Seip congenital lipodystrophy [BSCL] patients). This latter study was not considered suitable for the submission because oral zinc supplementation is not established clinical management for the treatment of LD, together with the study limitations (i.e small sample size and short treatment duration.)

Table 1: Studies identified in the clinical SLR and their inclusion or exclusion in the submission

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Metreleptin studies					
NIH 991265/20010796 (NCT00025883)					
1	Oral et al. 2002(1) Full publication	Prospective, open-label, single arm (4 months)	Patients with various forms of LD (N=9)	To determine whether leptin replacement improves the insulin resistance, diabetes, and hypertriglyceridemia of patients with LD	Study NIH 991265/20010769 was used to inform the clinical effectiveness and safety of metreleptin. Overall 16 published studies relating to this study were identified in the SLR (please note there was an error in Table C12 in the submission, which only cited 15 studies - the study by Chong 2009 had been accidently omitted.) However, the studies were (mostly) not specifically described in the submission. They were published while the study was ongoing and thus report on fewer patients than in an integrated CSR, which has been provided by Aegerion. The integrated CSR includes data from 107 LD patients (GL=66; PL=41; PL subgroup=31) and therefore is more statistically robust than these individual studies. A follow-up to this study (NIH-follow-up study) was used to inform the economic model.
2	Petersen et al. 2002(2) Full publication	Case control (3-8 months)	Patients with severe GL (fasting leptin concentration less than 4 ng/ml) associated with diabetes (N=3)	To examine whether or not leptin treatment might improve insulin sensitivity in LD patients	
3	Javor et al. 2005a(3) Full publication	Prospective, open-label, single arm (12 months)	GL patients (N=15)	To determine the long-term effects of leptin replacement in a cohort of LD subjects	
4	Oral, et al. 2006(4) Full publication	Prospective, open-label, single arm (4-8 months)	Patients with various forms of LD (N=10)	To study lymphocyte subpopulations and in vitro peripheral blood mononuclear cell activation during a study evaluating the effects of leptin on metabolic functions in severe LD (serum leptin levels <4 ng/ml).	
5	Musso, et al. 2005(5) Full publication	Prospective, open-label, single arm (8-12 months)	Patients with various forms of LD (N=14)	(a) Investigated the role of recombinant leptin therapy on the hyperandrogenic state and menstrual dysfunction of patients up to 1 year of treatment; (b) evaluated the effect of metreleptin on the growth hormone (GH) and insulin-like growth factor 1 (IGF-1) axis; (c) evaluated the pituitary-adrenal and thyroid axis over a 1-year period of metreleptin therapy; and (4) evaluated the effect of metreleptin therapy on the pituitary gonadal axis in a few male subjects to complement recent studies in male normal volunteers	

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
6	Park et al. 2007(6) Full publication	Prospective, open-label, single arm (12 months)	Patients with FPLD (N=6)	To investigate the role of low-dose recombinant leptin therapy in patients with FPLD to determine (1) the response of metabolic parameters to treatment, (2) the safety and tolerability of treatment over the long term, and (3) the differences of metabolic parameters at baseline and in response to treatment in patients with FPLD and GL.	
7	Chan et al. 2011(7) Full publication	Prospective, single-arm, open-label (12 months, but ongoing. Some patients have received up to 9 years of treatment up to July 2009 data cut)	Patients with acquired or inherited LD (N=55)	Evaluate the safety and effectiveness of leptin replacement therapy in patients with LD	
8	Joseph et al. 2014(8) Full publication	Prospective, single-arm, open-label (24 months)	Patients with various forms of LD (N=82)	To study the effects of metreleptin in TGs and HDL in LD in contrast to changes in TGs and HDL in interventions for the obesity-associated metabolic syndrome	
9	Christensen et al. 2014(9) Full publication	Prospective, single-arm, open-label (96-120 months)	Patients with CGL (N=31)	To study the effects of metreleptin on bone mineral content and mineral metabolism	
10	Chong et al. 2009(10) Full publication	Prospective, single-arm, open-label (96 months: metabolic outcomes at 12 months reported)	Patients with GL or PL (acquired or inherited) (N=48)	To determine whether leptin replacement in LD patients ameliorates their metabolic abnormalities over an extended period of time and whether leptin therapy is effective in the different forms of LD	
11	Brown et al. 2013(11) Abstract	Prospective, single-arm, open-label (12 months but on-going; as of a July 2011 data cut,	Patients with various LD subtypes (CGL, FPL, AGL, APL) (N=64)	To examine the effect of metreleptin on achieving commonly accepted therapeutic targets for HbA1c and TG reduction at a 12-month treatment time point	

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
		treatment duration was 2 month to 11 years including 64 patients treated for approximately 12 month or more)			
12	Muniyappa et al. 2013(12) Full publication	Prospective, single-arm, open-label (16-20 weeks)	Congenital or acquired LD (N=13)	To examine the early effects (16–20 weeks) of leptin replacement on B-cell function in patients with LD	
13	Diker-Cohen et al. 2015(13) Full publication	Prospective, open-label, single arm (12 months, but ongoing. Some patients have received up to 9 years of treatment up to July 2009 data cut)	GL or PL (N=86)	Evaluate the safety and effectiveness of leptin replacement therapy in patients with GL and PL	
14	Moran, et al. 2004(14) Full publication	Prospective, open-label, single arm (12 months)	Patients with various forms of LD (N=14)	To determine the effect of leptin replacement therapy in patients with LD on (1) body composition, comprising changes in fat and lean body mass and (2) bone density and serum markers of bone metabolism. In addition, the effects on liver volume and resting energy expenditure were determined	Used in Section 9.6.1.4.4 Effect of metreleptin on hyperphagia "As reported by Moran and colleagues from the NIH, metreleptin treatment of 14 patients with LD (12 with GL and 2 with PL) dramatically decreased food intake at 4 months from 3,170 kcal/day to 1,739 kcal/day." Please see the answer to question A15 for the background on these investigator sub-studies

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
15	Safar Zadeh et al. 2013(15) Full publication	Prospective, single-arm, open-label (Mean: 26 months; median 15 months, range 4–68 months)	Patients with GL or PL (N=27)	To study the spectrum of liver disease in LD and the effects of leptin replacement	The study by Safar-Zaheh was used in Section 9.6.1.4.3: Effect of metreleptin on hepatic enzymes, liver volume, and liver pathology The results of the study by Javor were not specifically included in the submission; however it showed that metreleptin significantly reduced triglycerides, transaminases, hepatomegaly, and liver fat content. These reductions were associated with significant reductions in steatosis and the hepatocellular ballooning injury seen in NASH. Please see the answer to question A15 for the background on these investigator sub-studies
16	Javor et al. 2005b(16) Full publication	Prospective, open-label, single arm (Mean 6.6 [range: 4-18] months)	GL (8 patients) or FPLD (2 patients) (N=10)	To examine the prevalence of NASH in LD patients with steatosis and to assess the histological changes in the context of biochemical and radiographic changes seen with metreleptin therapy.	
FHA101 (NCT00677313)					
17	Ajluni et al. 2016(17) Full publication	Prospective, single-arm, open-label (expanded access) (12 months)	Patients with PL and diabetes and/or hypertriglyceridemia with no pre-specified leptin level (N=23)	To determine the efficacy and safety of metreleptin among patients with PL using an expanded-access model	Study FHA101 was used as supportive evidence of the clinical effectiveness and safety of metreleptin. One publication relating to FHA101 was identified. However, the study not specifically described in the submission. Instead the integrated CSR, provided by Aergerion was used. includes data from 41 patients (GL= 9; PL=32; PL subgroup=7)
Metreleptin studies identified in the SLR but not included in the submission (with reason for exclusion)					
18	Beltrand et al. 2007(18) Full publication	Prospective, open-label, single arm (4 months)	Children with BSCL (N=7)	To test safety and efficacy of metreleptin treatment in children with BSCL before development of severe metabolic disease	Small sample size, short duration (4 months) study, only conducted in children (age range: 2.4-13.6 years)
19	Beltrand, et al. 2010(19) Full publication	Prospective, open-label, single arm (28 months)	Children with BSCL (N=8)	To assess the long-term efficacy and safety of leptin-replacement therapy to correct for the metabolic disorders.	Small sample size, only conducted in children (included 7 children from the above, short term trial).
20	Simha, et al. 2012(20) Full publication	A parallel group, open-label, observational study (6 months)	FPLD2 patients (N=24)	To compare efficacy of leptin therapy in FPLD patients with SH (serum leptin 7th percentile of normal) vs. those with moderate hypoleptinaemia (MH; serum leptin in 7th to 20th percentiles).	Small sample size only in patients with familial PL

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
21	Asthana, et al. 2015(21) Abstract	Prospective, open-label, single arm (16-32 weeks [4-8 months])	GL (N=9) or PL (N=8) (N=17)	To compare plasma angiopoietin-like protein 3 (ANGPTL3) and 4 in patients with LD and healthy controls and b) to examine the effects (16–32 weeks) of leptin replacement on ANGPTL 3 and 4	Small sample size, only an abstract (lack of information)
22	Brown, et al. 2015(22) Abstract	Non-randomised crossover study (19 days)	Previously leptin-treated (N=5, all GL, treatment duration 1-12y) and leptin-naïve (N=10, 9 PL) subjects (N=15)	To determine if leptin improves glucose and lipid metabolism in LD, independent of its effects on food intake.	Small sample size, only an abstract (lack of information)
23	Ebihara, et al. 2007(23) Full publication	Prospective, open-label, single arm (36 months)	GL patients (Japanese) (N=7)	To evaluate the efficacy and safety of long-term leptin-replacement therapy on seven Japanese patients with generalised LD.	Small sample size in Japanese patients (i.e different ethnic population than expected in the UK - see answer to question A17)
24	Schlogl, et al. 2016(24) Full publication	Prospective, open-label, single arm (52 weeks [12 months])	Patients with GL or PL (N=9)	Resting state functional MRI scans and extensive behavioural testing assessing changes in hunger/satiety regulation were performed during the first 52 weeks of metreleptin treatment in nine patients with LD	Small sample size
25	Vatier, et al 2016(25) Full publication	Prospective, open-label, single arm (compassionate therapeutic programme) (12 months)	Patients with various forms of LD (N=16)	To evaluate the effect of metreleptin on insulin sensitivity and insulin secretion using dynamic IV clamp procedures in 16 patients with genetic LD syndromes, included in a compassionate therapeutic programme	Small sample size
26	Araujo-Vilar, et al. 2015(26) Full publication	Retrospective, open-label study, single arm (Median 3 years [range 9 months to 5 years, 9 months])	Patients with genetic LD syndromes (N=9)	To determine the effectiveness of recombinant methionyl leptin (metreleptin) for improving glucose metabolism, lipid profile, and hepatic steatosis in patients with genetic lipodystrophy syndromes	Small sample size

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
27	Rodriguez, et al. 2014(27) Full publication	SLR and meta-analysis	LD not associated with the use of HIV protease inhibitors	A systematic review of the MEDLINE and Cochrane Library databases was conducted to identify studies assessing the effect of metreleptin on metabolic and hepatic endpoints of patients with lipodystrophy not associated with the use of HIV protease inhibitors	Systematic reviews were an inclusion criteria in the clinical SLR. Two publications from the same group reported the results of a systematic review and meta-analysis into the effects of metreleptin on metabolic and hepatic endpoints in patients with lipodystrophy syndromes not associated with the use of HIV protease inhibitors. In the full-text article by Rodríguez et al. 2014, 12 studies were included after full-text review of the papers identified in their literature search of Medline and the Cochrane library. All of these papers have been included in the current SLR reported here i.e. Beltrand et al. 2007 and 2010; Chan et al. 2011; Chong et al. 2009; Ebihara et al. 2007; Javor et al. 2005b; Moran et al. 2004; Oral et al. 2002; Park et al. 2007; Petersen et al. 2002; Safar Zadeh et al. 2013; and Simha et al. 2012. In the abstract by Paz-Filho et al. 14 studies were identified (the details were not reported). The results of the systematic review and meta-analysis were not considered relavant to the submission due to some limitations. In Rodríguez et al. a meta-analysis of results (N=226 patients across the studies)showed that metreleptin decreased FPG (0.75 standardised mean differences [SMD] units [range 0.36-1.13], P = 0.0001), HbA1c (0.49 [0.17-0.81], P = 0.003), triglycerides (1.00 [0.69-1.31], P < 0.00001), total cholesterol (0.62 [0.21-1.02], P = 0.003), liver volume (1.06 [0.51-1.61], P = 0.0002) and AST (0.41 [0.10-0.73] P =0.01). However, the review has several limitations, particularly that several of the studies from NIH 991265/20010796 were included
28	Paz-Filho, et al. 2014(28) Abstract	SLR and meta-analysis	LD not associated with the use of HIV protease inhibitors	A systematic review of the MEDLINE and Cochrane Library databases was conducted to identify studies assessing the effect of metreleptin on metabolic and hepatic endpoints of patients with LD not associated with the use of HIV protease inhibitors	

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
					individually but they may have included some of the same patients. In Paz-Filho et al. a meta-analysis of results from clinical studies in 243 patients showed that metreleptin decreased FPG [0.76 SMD units (range 0.40-1.12), P < 0.0001], HbA1c [0.55 (0.23-0.86), P = 0.0006], triglycerides [1.12 (0.81-1.43), P < 0.00001], total cholesterol [0.62 (0.21-1.02), P = 0.003), liver volume [0.98 (0.52-1.43), P < 0.0001], liver fat [0.67 (0.44-0.89), P < 0.0001], ALT [0.44 (0.07-0.80), P = 0.02] and AST [0.45 (0.17-0.73) P = 0.002].
Comparator study					
29	Dantas de Medeiros Rocha, et al. 2010(29) Full publication	Prospective, open-label, single arm	BSCL patients (N=10)	To evaluate the effect of diet intervention and oral zinc supplementation on the metabolic control of BSCL patients	This study was not considered suitable for the submission because oral zinc supplementation is not established clinical management for the treatment of LD, together with the study limitations i.e small sample size and short treatment duration.

Abbreviations: AGL = acquired generalised lipodystrophy; APL = acquired partial lipodystrophy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSCL = Berardinelli-Seip congenital lipodystrophy (also known as CGL); CGL = congenital generalised; CSR = clinical study report; FPG = fasting plasma glucose; FPL = familial partial lipodystrophy; FPLD = familial partial lipodystrophy, Dunnigan variety; GL = generalised lipodystrophy; HDL = high-density lipoprotein-cholesterol; IV = intravenous; LD = lipodystrophy; MRI = magnetic resonance imaging; MH = moderate hypoleptinaemia (serum leptin in 7th to 20th percentiles); NASH = non-alcoholic steatohepatitis; PL = partial lipodystrophy; Pts = patients; SD = standard deviation; SH = severe hypoleptinaemia (serum leptin 7th percentile of normal); SMD = standardised mean differences; TG = triglycerides

A4. Please provide full details of any search strategies used to identify comparator and/or natural history studies.

Response: The clinical SLR was carried out to search for trials of both metreleptin and trials of relevant comparators (see Section 9.1 of the submission). The objective of the SLR was to systematically search and review all available evidence on the clinical effectiveness (including the impact on clinical and metabolic outcomes) associated with metreleptin as an adjunct to diet as a replacement therapy and relevant comparators for the treatment of LD.(30)

Electronic databases were searched to identify relevant published studies, including Ovid MEDLINE and MEDLINE In-Process; Ovid EMBASE; Database of Abstracts and Review of Effects; The Cochrane Library, including the Cochrane Database of Systematic Reviews and the HTA Database; NHS Economic Evaluation Database; and the grey literature (see Appendix Section 17.1 and Question A1). In addition, internal sources at Aegerion associated with ongoing clinical studies (e.g. Natural History study in LD, NIH sub-studies, early access programme related studies) and unpublished clinical study reports were to be provided by Aegerion and assessed.

The inclusion criteria described in Table C11 Section 9.2.1 in the submission (and shown below for ease of review) was used to select studies from the published literature and unpublished studies. Studies considering any interventional treatment were included in the inclusion criteria, and therefore both metreleptin studies and possible comparators could be identified. From the searches of relevant published studies, one publication reported on a study evaluating individualised diets with oral zinc supplementation.(29) The study was a prospective, open-label, single arm study in 10 patients with CGL conducted over a 3-month period. Because oral zinc supplementation is not established clinical management for the treatment of LD, together with the study limitations (small sample size and short treatment duration), it was not considered suitable for the submission. During the selection of studies, natural history studies were considered as non-interventional studies (an exclusion criteria), and were therefore excluded and not included in the PRISMA diagram. However, in the absence of any suitable studies identified in the clinical SLR, data from the Natural History study in LD, provided by Aegerion, was used to inform the economic model (also see priority question A11).

Table 2: Table C11: Selection criteria used for published and unpublished studies

Inclusion Criteria	
Population	Patients with congenital or acquired GL, in adults and children 2 years of age and above Patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA1c ≥6.5 %, in adults and children 2 years of age and above Patients with rare LD syndromes (e.g. Donohue syndrome, mandibuloacral dysplasia (type A and type B) and Wiedemann Rautenstrauch syndrome), in adults and children 2 years of age and above
Interventions	Studies considering an interventional treatment

Outcomes	Clinical outcomes, including (not limited to): distribution of fat (% fat loss across face and neck, abdomen, thorax, upper limbs and lower limbs and number of fat sparing across face and neck abdomen, upper limb, lower limb, palms and soles), menstrual irregularities (polycystic ovaries etc.), hirsutism, growth, treatment related adverse events and mortality associated with LD and comorbidities associated with underlying disease Metabolic outcomes, including (not limited to): blood glucose (fasting glucose mg/dl), serum insulin (insulin (uIU/ml), HbA1c %, lipid profile (triglycerides mg/dl, total cholesterol mg/dl, HDL-C mg/dl and LDL-C mg/dl), liver function tests (AST U/L, ALT U/L), alkaline phosphatase (U/L), blood urea nitrogen (mg/dl), creatinine (mg/dl) and leptin (ng/ml) Metabolic complications, including (not limited to): diabetes, hypertriglyceridemia, insulin resistance and acute pancreatitis Quality of life outcomes if measured within the trial, including standardised and non-standardised outcomes
Study design	RCTs, non-RCTs (e.g. single arm trials, real world/observational studies), pooled analyses, retrospective analyses, long-term extension phase studies, systematic reviews/meta-analyses Ongoing clinical studies and unpublished reports available internally at Aegerion Pharmaceuticals (unpublished)
Language restrictions	None
Search dates	Journal articles, reports and summaries: No restrictions Conference abstracts published within the last four years (January 2013-January 2017, inclusive)
Exclusion Criteria	
Population	HIV-associated LD LD secondary to drug administration (insulin growth hormone, steroids, antibiotics and vaccinations) LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections LD in children <2 years of age
Interventions	Studies considering a non-interventional treatment
Outcomes	Studies reporting symptoms or short-term outcomes only Key search terms including: anatomy, histology, diagnosis, genetics, preclinical and reaction time
Study design	Phase 1 RCTs Study protocols Abstract with more recent existing full text publication Abstract or paper with insufficient reporting on population, study type or outcomes Healthy volunteer studies Animal studies Editorials/letters General reviews (other than systematic reviews)
Language restrictions	-

Search dates	Conference abstracts published before 2013
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; HIV,Human immunodeficiency virus; LD, lipodystrophy; LDL-C, low density lipoprotein cholesterol; RCT, randomised controlled trial	

A5. Please explain why HIV-associated LD was considered as an exclusion criterion in the searches in the clinical effectiveness (e.g. Table C11) whereas in the cost-effectiveness, studies focusing on HIV-associated LD were selected for data extraction.

Response: Due to the lack of expected economic/HRQoL evidence associated with non-HIV associated LD, the searches for the cost-effectiveness considered broader inclusion criteria including HIV-associated LD. Indeed, no publications were identified relating to non-HIV associated LD.

The objective of the clinical effectiveness systematic literature review was to systematically search and review all available evidence on the clinical effectiveness associated with metreleptin as an adjunct to diet as a replacement therapy and relevant comparators for the treatment of LD. Therefore, HIV-associated LD was considered an exclusion criteria because metreleptin is not indicated in this population.

A6. Priority Question: Please provide copies of all tables, figures and graphs referred to, but not included in the text of the CSRs:

a) NIH 991265/20010769 (NCT00025883). Open-label, single-arm study conducted at the NIH in the US.

b) FHA101 (NCT00677313). Open-label expanded access study designed to provide metreleptin under a treatment IND protocol for the treatment of patients with diabetes mellitus and/or hypertriglyceridaemia associated with LD.

Response: The full CSRs are being provided, including the sections of all the tables, figures and graphs referred to, but not included in the text of the CSRs.

A7. Priority Question: Please provide detailed explanation/justification why data reported in the clinical effectiveness section of the CS were not used to inform cost-effectiveness analysis and, conversely, why the clinical effectiveness evidence used in the cost-effectiveness analysis is not reported in the clinical effectiveness section of the CS. The cost-effectiveness analysis appears to be based on two studies (NIH Follow-Up study and Natural History study) which are not included in the clinical effectiveness section of the CS. Similarly, the reported methods for the cost-effectiveness analysis do not describe whether/how the data described on the clinical effectiveness section (e.g. changes in HbA1c and changes in triglycerides) were used to inform the cost-effectiveness analysis.

Response: In filing the dossier, only clinical trials were included in the clinical effectiveness section of the CS. However, i) the NIH pivotal trial reported in the CS and the NIH FollowUp study are not independent studies, and, as the question from the reviewer highlights, ii) both the NIH Follow-Up study and the Natural History study capture and analyse extensive

clinical information. The NIH Follow-Up study includes all the patients treated with metreleptin at NIH (at the time it was conducted), and incorporates the characteristics and outcomes for all patients enrolled in the NIH pivotal trial study, including changes in HbA1c and triglycerides. As such, the NIH pivotal trial data are part of the NIH Follow-Up study data that were used to inform the cost-effectiveness analyses. One of the primary objectives of the NIH Follow-Up study was to build on the NIH pivotal trial and extend it in two ways: a) increase the patient sample size (from 107 to 112), and b) expand the outcomes evaluated from biomarkers such as HbA1c and triglycerides to more direct measures of clinical burden for patients including hyperphagia, organ abnormalities, physical appearance, ability to perform work/school, mortality, etc. Both HbA1c and triglyceride values were used as factors potentially affecting patient utilities (see DCE analysis).

A8. Please also explain how the GL/PL Natural History study, used to provide control group data for the cost-effectiveness analysis, was selected. Was a literature review conducted? If yes, please provide a full search strategy with results. Also, please state if there were other sources that could have been used and, if so, on what basis was this study preferred?

Response: A review of the literature was conducted and leading lipodystrophy experts in the US, Brazil and Turkey were consulted. However, due to the rarity of GL and PL, insufficient data were available from the literature to provide adequate information to characterize the natural course of the disease, quantify its burden, and provide a control for the metreleptin studies. Key limitations included:

- Limited sample sizes of previous studies. Most studies on lipodystrophy are based on a very limited number of patients and typically from a single treatment centre.
- Limited information on key outcomes of interest:
    - Limited information on mortality. For example, a recent systematic literature review of the literature conducted by Gupta et al. (2016) provided the first estimates of the mortality impact of GL and PL in a large cohort of patients. However, the results were of limited usefulness for comparison vs. the experience on metreleptin as mostly limited to reporting mean age of death among patients who passed away.
    - Lack of longitudinal information. Typically, studies provide only information on one or two-time points (e.g. baseline and/or end of study period).
    - Lack of patient-level information (e.g. so that can baseline data can be used to control for differences across patients e.g. in terms of demographics, etc.)

By contrast the Natural History study is a large multi-centre study addressing the needs for most key outcomes of interest.

- 236 patients from 3 countries (US, Brazil, Turkey) and 5 treatment centres (NIH, University of Michigan, Dokuz Eylul University, Sao Paulo University, Federal University of Ceará). Note: When the cost-effectiveness analyses were filed in January, the data collection for Brazil (58 patients) was not completed, so only data from 178 patients was used.
- This study is the first to quantify survival patterns for lipodystrophy patients (see for example Akinci et al. 2017).

- The study provides detailed longitudinal, patient-level information for outcomes including organ abnormalities, physical appearance, reproductive function (for female patients), HbA1c/triglyceride and other laboratory values, etc.
- The study's detailed information provided the means to attempt a comparison vs. the patterns observed for metreleptin patients (e.g. in terms of organ abnormality progression and/or mortality).

A9. **Priority Question**: Please provide copies of any reports or other data sources relating to the ongoing studies, referred to in section 4.1 of the CS which were used as the source of clinical evidence for cost-effectiveness analysis:

- NIH Follow-Up study
- GL/PL Natural History study

Response: We are providing preliminary study summary reports and patient level data for both studies. Please note that both studies are still underway, but the summaries and datasets reflect the data used in the cost-effectiveness model. [GL-PL-NaturalHistory.zip and NIHFollow-upStudy.zip]

A10. Priority Question: Table A1 under the heading 'Rationale for variation from scope' indicates that the relevant PL population is those within the following age group: adults and children 12 years of age. However, Tables C16 and C17 (CS, pages 83 and 84) defined the PL subgroup as 'patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L' and 'patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L,' respectively i.e. there is no mention of an age-related subgroup.
For studies NIH 991265/20010769 and FH101 please provide subgroup data to match the expected licensed indication, as described in table A1 (CS, page 19) under the heading 'Rational for variation from scope.' Please also provide these data for the studies used to inform the cost-effectiveness analysis (NIH Follow-Up study and GL/PL Natural History study).

Response: The age range for the PL subgroup in study NIH 991265/20010769 was 15-64 years (see Table C16 in the submission) and for study FH101 it was 23-57 years (see Table C17). Therefore, although the age was not part of the original definition of the PL subgroup, the subgroup that is presented in the submission fits within the expected indicated age range (i.e. in adults and children 12 years of age and above). The youngest PL patient in the NIH Follow-Up study was 15 years old and thus the restriction to children at least 12 years of age was not binding. The group of PL patients included in the CE model base case are those who meet the PL subgroup definition (including age).

Partial lipodystrophy (PL) patients in the Natural History study were selected on the basis of medical diagnoses as reported by treating physicians during the observation period (i.e., acquired partial lipodystrophy or familial partial lipodystrophy). There was no distinction made between "severe" PL and "non-severe" PL. This created a group of patients which, as a whole, was likely less severe than PL patients at whom metreleptin treatment is targeted. Only 5 PL patients in the Natural History study were not observed after age 12 for at least part of the study, including 2 patients from Turkey and 3 cared for at NIH. Of these, only 1 met the criteria for the PL subgroup based on HbA1c and triglyceride levels.

A11. Priority Question: The scope defines the comparator as 'established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes)'. Please explain how studies for this comparator were sought and selected and provide full results. If data for any other comparator are available then please also provide a comparison with the results from the metreleptin studies, using either a naïve comparison or an adjusted comparison.

Response: Please see the answer to Question A4 for the details of the SLR conducted to identify relevant comparator studies. In the absence of any suitable studies identified in the clinical SLR, data from the Natural History study in LD was used to inform the economic model. The Natural History study is a retrospective, observational chart review study of LD patients from multiple sites in several countries (US, Turkey, Brazil). A total of over 175 patient histories have been evaluated to date, some with records covering >10 years. These patients have been treated with standard of care (SoC) and have not received metreleptin. The long duration of data availability as well as the large number of patients (in the context of an ultra-orphan disease) provided information on the natural history of disease in LD. Data extracted from charts for use in the economic analysis includes disease attributes such as levels of leptin, triglyceride, and HbA1c, appearance and progression of organ damage, female reproductive dysfunction, and death.

A12. The clinical effectiveness section of the CS includes no data or only very limited data for the effectiveness regarding a number of the clinical outcomes specified in the scope.
No data: liver cirrhosis; complications of diabetes; organ damage (including heart and kidneys); mortality (other than as an AE); pancreatitis (other than as an AE) effects on appearance.
Partial/very limited data: use of drugs other than diabetes therapies; growth and development; reproductive dysfunction; infection. Please confirm that no additional data are available for these outcomes, either from the NIH follow-up study, from publications related to NIH 991265/20010769 (NCT00025883) or FHA101 (NCT00677313), from the EAP, or from any other study/source of which you are aware. If data is available, please provide this in your response.

Response: The NIH Follow-Up study included many of these clinical outcomes and they are incorporated into the CE model. The patient level data set and the NIH study summary tables have been provided [NIH Follow-Up Study.zip] and include information regarding liver cirrhosis, heart and kidney abnormalities, pancreatitis, impaired physical appearance, and reproductive dysfunction. Only limited data was collected on infections (due to chart data limitations). No data was collected on growth and development. Please also see our response to A7.

A13. Priority Question: The section of the CS dealing with safety and adverse events includes the following text:
'Across the 148 patients included in LD studies, 6 (4%) patients (4 with GL and 2 with PL), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and hypertriglyceridaemia. One of the patients who developed septic shock concurrent with pancreatitis died; the other 5 patients recovered and continued on treatment. Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. The mechanism for

pancreatitis in these patients was presumed to be return of hypertriglyceridaemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridaemia.'
Given the reported non-compliance rates of between 9 and 19%, please explain/justify why the increased risk of pancreatitis on discontinuation of therapy is not considered in the cost-effectiveness analysis.

Response: Thank you for raising this important issue. The increased risk of pancreatitis due to discontinuation are captured by the CE model although not as a distinct entity. The methodology and rationale are described below. As described in our response to B1, patients who are observed to discontinue metreleptin in the NIH Follow-Up study (used to populate the "RWD" tabs in the model) or who are simulated to discontinued after the end of observation are assumed to develop additional organ abnormalities more quickly than patients who remain on metreleptin. As pancreatitis is one of the possible organ abnormalities tracked in the model, increased pancreatitis risk is incorporated.

A14. Please confirm that no data are available about the incidence of pancreatitis in patients who remain on treatment, i.e. does continuous treatment reduce the risk of pancreatitis?

Response: Data regarding the incidence and prevalence of pancreatitis are available in the NIH Follow-Up study, although these data were collected retrospectively. Nearly all patients who experienced acute or chronic pancreatitis prior to metreleptin treatment did not continue to experience pancreatitis while on treatment. Of the six patients who did experience one or more episodes of pancreatitis after metreleptin initiation, a clinician noted that two experienced events while non-compliant and two experienced events when metreleptin was temporarily discontinued. Patient level data regarding pancreatitis prevalence pre and post metreleptin is included in the NIH Follow-Up study dataset [NIH Follow Up Study.zip]

A15. The CS reports some limited data, from the NIH 991265/20010769 (NCT00025883) study population, on hyperphagia (section 9.6.1.4.4 of the CS) and on liver pathology (section 9.6.1.4.3 of the CS). These outcomes are not listed in the protocol for NIH 991265/20010769 (NCT00025883) and appear to be derived from separate 'mini studies' conducted by investigators. Please clarify.

Response: Study NIH 991265/20010769 was a retrospective Investigator-sponsored study with some limitations in the completeness of the study data, due primarily to several changes in sponsors over the 14-year development period of metreleptin. The development of metreleptin was initiated in the 1990s by Amgen as a treatment for obesity; the program was discontinued by Amgen as metreleptin monotherapy failed to show meaningful efficacy for weight loss. Concurrent with the Amgen evaluation of metreleptin in obesity, Dr. Philip Gorden at the National Institutes of Health (NIH) in Bethesda, MD initiated an Investigator-sponsored evaluation of metreleptin for the treatment of patients with clinically significant LD (NIH 991265 followed by study NIH 20010769). The trial was conducted at the NIH (Dr. Phillip Gorden, main site) and University of Texas Southwestern (UTSW) (Dr. Abhimanyu Garg). The sites followed a common protocol with the intent to publish data together but could pursue separate site-specific endpoints under different protocols, which included the studies on hyperphagia and liver pathology (Aegerion does not have access to the protocols

or the data, other than what has been published). In 2006, metreleptin was licensed to Amylin Pharmaceuticals who initiated retrospective collection of data from the NIH studies in order to pursue marketing applications for the LD indication. The US FDA approved metreleptin for the treatment of patients with GL on 24 February 2014, and metreleptin was subsequently sold to AstraZeneca. Aegerion Pharmaceuticals acquired metreleptin in January 2015.

A16. Section 6.2 (CS, page42) states: 'There is limited published data available on the incidence and prevalence of LD in England. One study (Chiquette et al. 2017) identified in the literature search was considered but was not deemed accurate or generalisable for a UK population and the anticipated metreleptin licence. More relevant and accurate estimates are available based on EAP data from a decade of metreleptin use in UK clinical practice at Addenbrooke's.' The ERG has noted that Chiquette et al. 2017 reported the range of worldwide prevalence of all LD to be [redacted] cases/million, with [redacted] cases/million in the UK. Using figures from Addenbrooke's and population of England ([redacted] in 55 million) equates to [redacted] per million. The ERG notes this is a substantial 10-fold difference in the estimates derived from these two sources. Please justify why the estimates from Chiquette are not considered to be relevant and why the data from Addenbrook's is preferred.

Response: Chiquette et al. 2017 conducted a search of five electronic medical record (EMR) databases and literature searches to quantitatively estimate the prevalence of LD.(31) EMR and literature searches were conducted from 2012 to 2014. One of the EMR databases searched included the UK General Practice Research Database (GPRD) which, according to the publication, contained around 10 million UK patients based on a large sample of general practices. However, the search to determine LD patients from this database included a search for ICD-9-CM code 272.6 (diagnostic criteria often associated with LD) and, ≥2 diagnosis claims for type 2 diabetes mellitus (T2DM) or high triglycerides or chronic non-alcoholic liver conditions. While the Chiquette study allows an estimation of patient numbers associated with overall LD, the use of the stated ICD-9-CM code will likely overestimate patients due to being a nonspecific LD diagnostic code.

Another limitation of the Chiquette study is that prevalence figures are not reported by LD type. It is, however, likely that a large proportion of patients from the Chiquette study would be PL patients including the most prevalent form of PL – FPLD1 who do not have low leptin levels. The number of these potentially prevalent patients being within the proposed indication is expected to be significantly smaller. The study also does not include the entire geographical area of England or the UK, and hence could be over- or under-estimating figures as rare diseases such as LD may be more prevalent in certain geographical areas.(31)

The Chiquette study, as mentioned, also completed a literature search in May 2012 to identify the prevalence of LD in Europe. This resulted in estimates of prevalence taken from 89 papers reporting AGL, CGL, APL, and FPL. Figures were adjusted for underreporting and were extrapolated to the European Union community with assumptions adopted in the literature search to obtain a prevalence estimate which may result in overestimated prevalence figures. In particular, based on the study by Garg(32) (a clinical review based on a literature review and the author's knowledge of the field) it was estimated that only 25% of all LD cases are reported in the literature. Hence, the prevalence estimates were multiplied

by four, although it is unclear how this multiplier was derived or if it is an accurate assumption. Due to these limitations in both the EMR database data collection and the literature search, the prevalence figures were not deemed robust or generalisable enough for determining England and Wales prevalence of LD.

Data from Addenbrooke's may underreport the overall number of people with LD in the UK, especially those with FPLD1 who do not have low leptin levels, as they may be successfully treated locally and not referred to Addenbrooke's. However, these cases would not be eligible for metreleptin treatment under its expected indication. If metreleptin is approved for use on the NHS in England, the care of LD patients is expected to remain largely unchanged, with metreleptin continuing to be given to patients at Addenbrooke's where it will be prescribed within its marketing authorisation to patients with a clinical need. Therefore, with regard to the number of patients eligible for treatment with metreleptin, data from Addenbrooke's, where patients have been receiving metreleptin through an early access programme (EAP), is likely to be most the appropriate source; the EAP has been running for over 10 years and factors that may restrict patient access to the treatment such as price are reduced due to the EAP objectives of compassionate access from a LD centre of excellence.

A17: Please explain why Japanese patients are not relevant to this submission (CS, page 73)?

Response: Although the study by Ebihara, et al. was excluded, it did show that metreleptin was effective in Japanese patients: metreleptin dramatically improved fasting glucose ($P < 0.05$) and triglyceride levels ($P < 0.05$) within 1 week. Improvement of fatty liver, and feelings of satisfaction after a meal were also observed.(23) Four of five female patients who were of reproductive age had hypogonadotropic amenorrhea at baseline but resumed and sustained normal menses with metreleptin. The therapy was well tolerated, and its effects were maintained for up to 36 months without any notable adverse effects. However, another limitation with regards to this submission is that it only included 7 patients with GL.(23) Overall, we did not think that a study with a small sample size in Japanese patients would be of relevance to the submission.

A18. For Table C13 (CS, page 73), please provide a reason why each study was excluded.

Response: Please see below the studies listed in Table C13, together with the reason why the study was excluded.

Table 3: Table C13: Excluded published studies

Primary study reference	Study name (acronym)	Population	Intervention	Reason for exclusion
Beltrand et al. 2007 (18) Full publication	_	Children with BSCL (N=7)	Metreleptin	Small sample size, short duration (4 months) study, only

Primary study reference	Study name (acronym)	Population	Intervention	Reason for exclusion
				conducted in children (age range: 2.4-13.6 years)
Beltrand, et al. 2010 (19) Full publication	_	Children with BSCL (N=8)	Metreleptin	Small sample size, only conducted in children (included 7 children from the above, short term trial).
Simha, et al. 2012 (20) Full publication	NCT00457938	FPLD2 patients (N=24)	Metreleptin	Small sample size only in patients with familial PL
Asthana, et al. 2015 (21) Abstract	_	GL (N=9) or PL (N=8) (N=17)	Metreleptin	Small sample size, only an abstract (lack of information)
Brown, et al. 2015 (22) Abstract	_	Previously leptin-treated (N=5, all GL, treatment duration 1-12 years) and leptin-naïve (N=10, 9 PL) subjects (N=15)	Metreleptin	Small sample size, only an abstract (lack of information)
Ebihara, et al. 2007 (23) Full publication	_	GL patients (Japanese) (N=7)	Metreleptin	Small sample size in Japanese patients (i.e. different ethnic population than expected in the UK)
Schlogl, et al. 2016 (24) Full publication	_	Patients with GL or PL (N=9)	Metreleptin	Small sample size
Vatier, et al 2016 (25)	EAP	Patients with GL or PL (N=16)	Metreleptin	Small sample size
Araujo-Vilar, et al. 2015 (26)	EAP	Patients with GL or PL (N=9)	Metreleptin	Small sample size
Abbreviations: BSCL, Berardinelli-Seip congenital lipodystrophy; EAP, Early Access Programme; FPLD2, familial partial lipodystrophy, Dunnigan variety; GL, generalised lipodystrophy; PL, partial lipodystrophy				

A19. Please provide a) the number of UK patients in each of the included studies, b) how long each of the UK patients have received metreleptin, and c) how long they have been followed up. Please provide these data both for the studies included in the clinical effectiveness section of the CS [NIH 991265/20010769 (NCT00025883) and FHA101 (NCT00677313)], and for the studies used to inform the cost-effectiveness analysis (NIH Follow-Up study and GL/PL Natural History study).

Response: In NIH 991265/20010769 there was one patient from the UK (patient 901-026; 51 years, male, with AGL) who received metreleptin for 248 days (24/10/2003 to 27/06/2004). The patient was discontinued early because ineligibility was determined. Study FHA101 only included patients from the US. The NIH Follow-Up study also includes information for the same UK patient included in NIH 991265/20010769 (patient NIH-026). The Natural History study collected data for patients with lipodystrophy who were not treated with metreleptin at five locations: two in the US, one in Turkey, and two in Brazil (data collection in Brazil is ongoing). One patient from the UK, a female with APL diagnosed at age 42, was cared for at NIH and is included in the study.

A20. Please provide a reason why 8 GL patients were transferred to another program (e.g. lack of effect, AEs), noted in Table C18 (CS, page 87).

Response: The 8 GL patients, who were from outside of the US, were transferred to early access programs within their own country at the time of commercialisation of metreleptin in the US when the study was ending. Metreleptin was approved by the FDA in February 2014, and as of December 2014, all patients were either off metreleptin treatment or had transitioned to commercial product or early-access programmes (including the 8 patients mentioned).(33)

Section B: Clarification on cost-effectiveness data

Disease Progression

B1. Priority Question: In the model, most of the simulation calculations are based on the data in the “RWD_*” sheets but the data in these sheets are not clear.

Please explain how the RWD data provided in the cost-effectiveness model were generated and what each entry in the “RWD_*” sheets means.

Response: All data in the "RWD" tabs in the model are patient level data from patients observed in the NIH Follow-Up study. Some data elements (e.g., HbA1c levels, organ abnormalities) were documented at baseline and during the full follow-up time-period. Others were collected and analysed only at baseline, or only at baseline and during the first year after treatment.

Within the RWD tabs, the column labelled "0" refers to the pre-treatment baseline period, the column labelled "1" refers to the first year after treatment, and subsequent columns refer to subsequent years. The entry for each patient in each column reflects whether the attribute is present ("1") or absent ("0"). Once the patient is no longer observed, all subsequent columns will be blank, and further values are imputed on the "SIM" tabs.

(B1.a) For instance:

- What is difference between the data in “RWD_HeartAbnormal _hypertension” and the data in the “RWD_HeartAbnormal _nonhyper“ sheets? Additionally, please clarify how they are combined in the “RWD_HeartAbnormal” sheet. The ERG note that it appears to be based on a control on the “enable alternate scenario”, in cell “B9” from “Background Lookups and Calcs” sheet, but could not identify the original checkbox.

Response: RWD_HeartAbnormal_Hypertension resolves heart abnormalities present at baseline in period 1 for patients who were prehypertensive at baseline and have normal blood pressure in period 1. Specifically, this means a small number of patients with a value of 1 for heart abnormality in period 0 have a value of 0 for heart abnormality in period 1. Data from the NIH Follow-Up study does not otherwise track resolution of heart abnormalities, and thus improvement in blood pressure was used as a proxy. Only improvements in prehypertensive patients were considered as improvements in patients with stage 1 or 2 hypertension may have been due to increased use of anti-hypertensive medications. RWD_Heart_Abnormal_nonhyper is the default input sheet and does not infer an improvement in heart abnormalities from an improvement in hypertension for any patients. When the "Alternative Scenario" is activated on the Cost-Effectiveness tab, RWD_Hearth_Abnormal_nonhyper values are replaced with RWD_HeartAbnormal_Hypertension values for all patients in the RWD_HeartAbnormal sheet.

- **(B1.b)** In some patients, the number of organ abnormalities decreased in time, for instance, for patient 1, liver, kidney and pancreas abnormalities present at baseline seems to be resolved after the first year. Please explain the reasons of these type of organ impairment improvements, as they were not considered in modelling of the organ abnormality progression, explained in Section 17.6 (total number of organs assumed to stay the same or increase in time).

Response: Improvement in kidney and liver abnormalities were assigned to patients with proteinuria (kidney) or impaired hepatic function (liver) based on a reduction of at least 20% of previously abnormal laboratory readings for protein excretion (kidney) and ALT/AST (liver) in the year after metreleptin treatment. As specific types of abnormalities did not account for all kidney and liver abnormalities, only a subset of patients could be identified as experiencing a resolution of their abnormality after metreleptin treatment. Clinical notes suggested that other types of liver and kidney abnormalities also resolved, but as we did not systematically observe such notes, we chose to limit resolution of kidney and liver abnormalities to those that could be tracked in laboratory data.

As laboratory data for protein excretion and ALT/AST were not available as a time series in the natural history data, we chose to only track the development of organ abnormalities and not subsequent resolution in the organ progression and survival analysis.

The only type of pancreatic abnormality included in either the organ progression / survival analysis or the CE model was pancreatitis. An NIH nurse reviewed patient records for evidence of pancreatitis prior to metreleptin initiation and identified which patients experience no re-occurrence of pancreatitis after metreleptin initiation.

Improvement in heart abnormalities could not be easily identified in the data and as hypertension was not considered to be an abnormality for the purpose of organ progression / survival modelling, we assumed that all heart abnormalities present at baseline continued to be present after treatment initiation. The "Alternative Scenario" relaxes this assumption by assuming that certain patients whose hypertension resolved after treatment experienced a resolution of their heart abnormalities.

- **(B1.c)** Data in the “RWD_Hypoevents”: please confirm if this relates to the total number of hypoglycaemia events patient experienced in that year.

Response: Yes, this value documents the number of hypoglycemia events that occur for each treated patient in each year, and is based directly on adverse event data tracked at NIH.

- **(B1.d)** Data in the “RWD_Attributes” sheet: two measurements for each attribute (hyperphagia, ability to work, etc.) For each attribute, the values under “0” column are used for the SoC arm patients and the values under the “1” column are used for metreleptin arm patients. It is stated in the company submission that the values under the “1” column indicate the improvement from the baseline, however the details on the size/characteristics of these improvements are not provided. Please provide more detailed information on these attributes. What does “0” and “1” as attribute values mean exactly? What does the composite improvement indicator mean and when/how it is measured? Why were the improvements in these attributes not presented in the clinical effectiveness part of the submission?

Response: The 0 column contains each patient's attribute status at baseline while the 1 column contains each patient's attribute status in period 1 of treatment.
An attribute value of 0 indicates the absence of that attribute while a value of 1 indicates the presence of that attribute. Attributes that are present in period 0 are coded as absent in period 1 if the real-world data from the NIH Follow-Up study indicated that the patient has improved as of the patient's last NIH visit.

Hyperphagia and Impaired ability to work/attend school were coded directly from clinician's notes indicating the presence or absence of these attributes before metreleptin treatment and the improvement of the condition after metreleptin treatment. Improvement in impaired physical appearance was determined by improvement in any of acanthosis nigricans, hyperkeratosis, or hirsutism by the last NIH visit date. Improvement in disruption to female reproductive function is determined by improvement in any of irregular menstruation or polycystic ovary syndrome (PCOS) by the last NIH visit date. For an underlying issue to be improved as of the last visit date, the patient must have had the issue at baseline, and cannot have experienced any new emergent issues in the follow-up period specifically for that issue. In the case that one underlying issue present at baseline did not improve, while another issue present at baseline did improve, the patient is considered to have improved.

The clinical effectiveness portion of the submission focused specifically on data from the single arm trial and did not include the additional information from the follow-up study that

was needed for longer-term economic modelling. Please also see our response to question A7.

- **(B1.e)** Data in the “RWD_Discontinuation” sheet: Please explain the figures in this sheet. Please explain whether 0 means that the patient discontinued? What does a value between 0 and 1 mean (like 0.11 in cell X22). Does it mean that the patient continued the medication 11% of time? Why is the 1st year discontinuation not included in calculations? Please explain the calculations that yielded 2.045% as the overall discontinuation rate and explain what the main reasons for the discontinuation were (e.g. lack of efficacy, neutralizing antibodies, side effects).

Response: In the RWD_Discontinuation sheet, 0 means a patient did not receive metreleptin treatment at any point while 1 represents a full-year of metreleptin treatment. Values between 0 and 1 represent the proportion of year on which a patient received metreleptin treatment (e.g. a patient who received treatment for 30 days would be coded as ~.08 (= 30/365.25)

The 2.047% discontinuation rate used in the model is the weighted average annual discontinuation rate of metreleptin patients observed in the real-world data when period 1 is excluded, where each period is weighted by the number of patients who are still under observation. Period 1 was excluded from this calculation because observed discontinuation data are available for period 1 (as patients have all been observed for at least one year after treatment initiation) and because the pattern of discontinuation in the short term (<1 year) may be substantially different than in the long run.

- **(B1.f)** Data in the “RWD_Leptin” sheet: please explain why only baseline values are provided?

Response: The model uses baseline leptin values as a variable in its identification of patients within the proposed treatment label. The model does not use non-baseline values in any calculation, so they have not been included.

B2. **Priority Question:** The RWD data presented in “RWD_*” sheets are used in the calculations given in the “SIM_*” sheets, while simulating the disease progression. However, calculations in these sheets are not clear. Please explain the calculations in the “SIM_*” sheets, for instance:

- **(B2.a)** Please explain, step by step and cell by cell, how the probabilities of 0, 1, 2, 3 and 4 organ abnormalities and the average number of abnormalities were calculated both for metreleptin and SoC patients and the reason of using “buffer” calculation sheets (e.g. SIM_NumOrgansAbnormal and SIM_NumOrgansAbnormal_Buffer sheets) and sheet for flagging issues (“SIM_Flag”).

Response:

1. The calculation of organ abnormality progression begins with the sheets containing real-world data on each patient's organ abnormality level (RWD_HeartAbnormal, RWD_KidneyAbnormal, RWD_LiverAbnormal, RWD_PancreasAbnormal). In each of

these sheets, each patient is coded either a 0 (no abnormality present) or a 1 (abnormality present) both at baseline and in each treatment period.

2. Coded values in the real-world tabs are translated into probabilities in the Prob_KidneyAbnormal, Prob_HeartAbnormal, Prob_LiverAbnormal, Prob_PancreasAbnormal tabs. These tabs are only used to provide baseline probabilities for MET patients but are used to provide probabilities of each organ abnormality at baseline and post-treatment for SOC patients. This is due to the fact SOC patients are assumed to retain any organ abnormalities at baseline, so baseline probabilities are simply carried forward to end of the time horizon. For example, a SOC patient with a 1 at baseline in the RWD_KidneyAbnormal tab will be assigned a 100% value for periods 0-60 in the Prob_KidneyAbnormal tabs.
3. The calculation of each patient's probability of attaining 0,1,2,3 and 4 organ abnormalities under both MET and SOC treatment begins in the sheets SIM_Prob 0OrganAbnormalBuffer, SIM_Prob 1OrganAbnormalBuffer, SIM_Prob 2OrganAbnormalBuffer, SIM_Prob 3OrganAbnormalBuffer, SIM_Prob 4OrganAbnormalBuffer.
    a. For periods in which a MET patient's real-world organ abnormality is available, the probability of a patient attaining 0,1,2,3, or 4 organ abnormalities is determined by the real-world data (e.g. a patient that has heart and liver organ abnormalities but no pancreas and kidney abnormalities in period 1 of the NIH trial will be coded as having a 100% probability of two organ abnormalities in SIM_Prob2OrganAbnormalBuffer in period 1 and a 0% probability of attaining other organ abnormality levels).
    b. For periods in which a MET patient's real-world organ abnormality data is unavailable, the probability of a patient attaining a certain organ abnormality level is a weighted average of two products: 1. the product of the previous period's probability, the relevant organ abnormality transition probability for MET patients (whether for PL or GL), and the probability of remaining on MET treatment (SIM_Discontinuation). 2. The product of the previous period's probability, the relevant organ abnormality transition probability for SOC patients (whether for PL or GL), and the probability of discontinuation (1-SIM_Discontinuation).
    c. For SOC patients, the probability of a patient attaining 0,1,2,3, or 4 organ abnormalities is the product of the previous period's probability and the relevant organ abnormality transition probability for SOC patients (whether for PL or GL).
4. SIM_NumOrganAbnormal_Buffer contains initial estimates of patient organ abnormality level in each period based on probabilities calculated in step 3.
5. In SIM_Prob 0OrganAbnormal, SIM_Prob 1OrganAbnormal, SIM_Prob 2OrganAbnormal, SIM_Prob 3OrganAbnormal, SIM_Prob 4OrganAbnormal, an adjustment is made to the probability estimates of SOC patients identified in SIM_FLAG as having fewer organ abnormalities (at least 1 less) than their MET counterpart ("TRUE" in SIM_FLAG). In the few patients in which this occurs (~11 patients), the SOC patient is coded with the same organ abnormality level as his or her MET counterpart.
6. SIM_NumOrgansAbnormal contains final per-period estimates of each patient's organ abnormality level based on probabilities calculated in steps 3 and 5. Expanding upon the identification in SIM_FLAG, SOC patients with an organ abnormality level

estimate lower than their MET counterpart are coded with the MET organ abnormality level (this impacts the same 11 patients identified in SIM_FLAG).

- **(B2.b)** “SIM_hypoevents” sheet does not include any calculation, but includes only hardcoded data. Please explain what these data mean (indicating a source/assumption) and provide the calculations for the hypoglycaemic event extrapolations. Also please explain what assumptions were taken for the hypoglycaemic events under SoC.

Response: The values in SIM_Hypoevents are first derived from those in RWD_Hypoevents. For periods lacking real-world data, each patient is considered to experience the average number of annual events as determined by the real-world data. For example, data on Patient 2's hypoglycaemic events is only available for periods 1 and 2, in which the patient experienced 2 and 0 events respectively. Therefore, for periods 3 through 60, patient 2 is assumed to have experienced 1 hypoglycaemic event a year as that is the yearly average for patient 2 during the time when real-world data are observed.

- **(B2.c)** Please explain the simulation of the discontinuation as well as its implications in terms of cost, utility and transition probabilities.

Response: Patient discontinuation is first determined by the real-world data. In each period, patients are assigned their probability of continuing treatment as observed in the NIH Follow-Up study, with patients who continue treatment for the full period assigned 100%. For periods where no real-world data is available, each patient's probability of continuing metreleptin is the previous period's probability multiplied by (100% - 2.047%).
Patient drug costs in each period are defined as the cost of metreleptin plus SoC treatment multiplied by the probability of remaining on metreleptin plus SoC treatment multiplied by the probability of discontinuation.
The impact of discontinuation on organ abnormality transition is described in 3.b of answer to B.2 above (Description of organ abnormality progression calculation). In short, each patient’s level of organ abnormality in a period is a weighted average of their organ abnormality levels while on and off MET treatment (reflected in probability of discontinuation).
Discontinuation does not have a direct impact on utility decrements, but does affect the probability that a patient has certain attributes (e.g., organ abnormalities) and thus the probability the patient receives the decrement associated with that attribute

- **(B2.d)** In the simulation sheets for attributes other than organ impairment and blood glucose and triglyceride levels (e.g. “SIM_ParentalDisutility, SIM_ProgressionSpeed, SIM_Hyperphagia, SIM_Reprod1, SIM_Physapp” and “SIM_AbilityWork”), the corresponding data from the NIH Follow-Up study are used (can be seen in the “RWD_*” sheets). It seems that when the RWD data are missing, it is automatically assumed “0” in the simulation. Please clarify if this was a programming error or a deliberate assumption.

Response: When real-world data is absent at both baseline and in period 1, 0 is assumed in the simulation for the patient in both the SOC and metreleptin arm. This assumption is made

because attributes are defined so that "1" implies an impairment in condition, and we expect an impairment would likely be indicated in the patient's medical data. Thus, when we have no evidence of an attribute being present, we typically assume it is absent. The one exception to this is hyperphagia, which is unlikely to be documented for patients unless physicians are prospectively asked to assess it, whether or not it exists. We apologize for the programming error that resulted in assignment of a 0 in period 1 to patients with baseline but no period 1 data for hyperphagia. In the corrected model, patients with no hyperphagia data in period 1 are considered to experience the average treatment effect of metreleptin for their relevant group. For example, patients with hyperphagia at baseline who lack metreleptin treatment data now have a hyperphagia value of .09 in period 1 since 9% of patients in the real-world data that suffer from hyperphagia at baseline continue to have hyperphagia in period 1.

This update to the model does not appear to have a material impact on QALY/ICER estimates for key population groups. In fact, incremental QALYs for the label population decrease from 8.11 to 8.10, ceteris paribus.

B3. **Priority Question:** Please provide additional description of the methodology in deriving the transition probabilities and further justification for some of the assumptions around progression of organ abnormalities.

Response: The transition probabilities were derived separately for each observed transition (0 to 1 abnormalities, 1 to 2 abnormalities, etc) by fitting an exponential decay curve to a Kaplan Meier "survival" curve in which "survival" is defined as not developing an additional abnormality. The exercise was completed separately for each transition and each data set (NIH Follow-Up study, Natural History Study, and matched subset of Natural History Study).

To examine whether the estimated rates were different between the NIH Follow-Up study and the Natural History Study or matched Natural History subset, we pooled the data and estimated a Cox model for each transition that related to an indicator for treatment (1 for patients in the NIH Follow-Up Study). To further ensure that the slower rate of progression observed in the NIH Follow-Up Study was due to fewer patients developing abnormalities and not due to censoring due to death, we also ran a collection of cox models in which the transion outcome was defined at progression or death.

Cox Model Output Using Original Matching Approach and Original Data

Table 4: Cox Model Output Comparing NIH patients to Natural History Study patients

		Summary Statistics			Results		
Progression Event	Death Categorization	N	# Deaths	# Events	Coefficient	Hazard Ratio	Significance[1]
0 to 1	Censor	146	1	128	-0.8989	0.4070	(0.371)
	Organ			129	-0.2068	0.8132	(0.772)
1 to 2	Censor	164	2	117	-1.0717	0.3424	(0.019)*
	Organ			119	-0.9035	0.4052	(0.031)*
2 to 3	Censor	167	1	93	-0.6761	0.5086	(0.012)*
	Organ			94	-0.6848	0.5042	(0.011)*

3 to 4	Censor	125	12	37	-1.3406	0.2617	(0.001)**
	Organ			49	-0.8342	0.4342	(0.009)**

Note
1. * p<0.05, ** p<0.01

Table 5: Cox Model Output Comparing NIH patients to Matched Natural History Study patients

		Summary Statistics			Results		
Progression Event	Death Categorization	N	# Deaths	# Events	Coefficient	Hazard Ratio	Significance[1]
0 to 1	Censor	41	1	38	-1.0557	0.3479	(0.300)
	Organ			39	-0.3691	0.6914	(0.614)
1 to 2	Censor	56	1	45	-1.2427	0.2886	(0.009)**
	Organ			46	-1.0827	0.3387	(0.014)*
2 to 3	Censor	92	1	54	-0.8162	0.4421	(0.006)**
	Organ			55	-0.8340	0.4343	(0.005)**
3 to 4	Censor	85	12	24	-1.1588	0.3139	(0.010)*
	Organ			36	-0.6767	0.5083	(0.052)

Note
1. * p<0.05, ** p<0.01

Cox Model Output Using Original Matching Approach and Updated Data

Table 6: Cox Model Output Comparing NIH patients to Natural History Study patients

		Summary Statistics			Results		
Progression Event	Death Categorization	N	# Deaths	# Events	Coefficient	Hazard Ratio	Significance[1]
0 to 1	Censor	145	1	128	-1.1572	0.3144	(0.249)
	Organ			129	-0.4718	0.6239	(0.509)
1 to 2	Censor	168	2	119	-0.7503	0.4722	(0.054)
	Organ			121	-0.6278	0.5338	(0.087)
2 to 3	Censor	170	3	93	-1.0794	0.3398	(0.000)**
	Organ			96	-0.9955	0.3695	(0.000)**
3 to 4	Censor	127	11	35	-1.8678	0.1545	(0.000)**
	Organ			46	-1.3463	0.2602	(0.000)**

Note
1. * p<0.05, ** p<0.01

Table 7: Cox Model Output Comparing NIH patients to Matched Natural History Study patients

		Summary Statistics			Results		
Progression Event	Death Categorization	N	# Deaths	# Events	Coefficient	Hazard Ratio	Significance[1]
0 to 1	Censor	38	1	36	-1.4320	0.2388	(0.159)
	Organ			37	-0.7743	0.4610	(0.291)
1 to 2	Censor	57	1	43	-0.8901	0.4106	(0.031)*
	Organ			44	-0.7585	0.4684	(0.053)
2 to 3	Censor	91	3	50	-1.0854	0.3378	(0.000)**
	Organ			53	-1.0155	0.3622	(0.000)**
3 to 4	Censor	83	11	17	-1.4548	0.2334	(0.007)**
	Organ			28	-1.0518	0.3493	(0.007)**

Note
1. * p<0.05, ** p<0.01

The treatment indicator is significant for all transitions except for 0 to 1 (due to lack of observations in the NIH Follow-Up study), and the level of significance of the treatment indicator is the same across these two specifications in all but two cases. Cox Model Output Using Original Matching Approach and Original Data

Table 4 and **Error! Reference source not found.** reflect the statistical analyses of the transition rates included in the CS.

Subsuquent to our submission, we identified an inconsistency in the set of heart conditions considered abnormalities in the NIH Follow-Up study data used for the transition probability analysis, and those considered abnormalities in the Natural History data and the CE model. Specifically, hypertension was included as an abnormality for NIH patients in the previous version of this analysis. Additionally, this analysis did not include the most recent available data regarding pancreatitis. To addresses these issues, we have replicated the analyses using revised data that are consistent with the data used in the CE model "RWD" tabs. Please see our response to B11 for the revised matched Natural History cohort and transition rates. Table 6 and Table 7 show that the relationship between progression of organ abnormalities and treatment continue to hold in the revised data.

- **(B3.a)** Please clarify why the type of affected organ (pancreas, kidney, heart and liver) and the severity of an organ abnormality (e.g. ectopic fat deposit on an organ or an organ failure) were not taken into consideration in the analysis. Based on this assumption in the CS, the cost and health outcomes from an ectopic fat deposit around the liver are the same as those from a myocardial infarction or from a kidney failure. In addition, this level of abnormality accumulation overlooks the possibility of having more than one abnormality on the same organ (e.g. fat deposit on liver in addition to cirrhosis).

Response: We recognize that a model in which we characterize a patient's disease progression by a state vector that includes information about the identity of organs with abnormalities as well as the severity of these abnormalities would be more realistic. (34-36)

There are several reasons why we have opted to use only the count of organ systems with abnormalities in the progression and survival analysis rather than a more realistic approach that accounts for the specific organ and type and severity of impairment.

1) Data constraints: our affected organ abnormality data are generated based on a single-arm trial with 112 patients, and a chart review with 178 patients. A more complex model with, say, 17 health states (combination of no, and some level of abnormality for each of 4 organs, and death) instead of 6 would place untenable demands on the data.[1] Each patient is individually modelled as part of a cohort which evolves according to a Markov process. Increasing the number of states we specify to 17 would require estimating 256 transition probabilities, if we allow patients to transition from any state to any other state (excepting death).
2) Evidence from other CE models: While many other CE models have used larger state spaces, some CE models have found that for numerous disease states, smaller state spaces are sufficient to understand cost-effectiveness. Delea et al. estimate the cost-effectiveness of pazopanib versus sunitinib in renal cancer using a partitioned-survival analysis model with 3 health states (pre-progression, post-progression, and dead). Epstein et al. use three health states (alive, death from other causes, death from aneurysm causes) to estimate the long-term cost-effectiveness of repair options for aortic aneurysms. Clark et al. use three health states, based on degree of renal failure, to capture the cost-effectiveness of catherisation with different types of catheters.
3) Tractability of the CE model we generate: While a finer record of each patient's disease progression could provide more accurate predictions, the results we find with our existing approach allow for accommodation of our data limitations and provide sufficient validation that:
    a. The number of organs with abnormalities does have an effect on mortality (see Table 73 in the CS)
    b. Treatment does impact the rate at which patients accumulate abnormalities to their organ systems (see tables below).

    Additionally, while there are some differences in estimated utility decrements or additional costs by organ, a range of potential decrements and costs are explored in our sensitivity analysis.

Please also note that we do not claim that the number of impaired organs is the most important, or sole, indicator of disease progression. We merely argue that it is a measurable indicator that succinctly captures a patient's overall health state and provides a useful way to meaningfully estimate a treatment effect for metreleptin beyond the 15 years of data observed in the NIH Follow-Up study.

[1] The 6 states in our current model correspond to (1) "alive with 1 organ abnormality", …, (4) "alive with 4 organ abnormalities", (5) "alive with no organ abnormalities", and (6) "deceased". A model in which the identity of the organ matters would include at least 17 states, since each of 4 organs would either be impaired or not (hence 2^4 possible states) and death. Levels for the severity of impairment would add states at an exponential rate.

The results of Cox models predicting transition events without other covariates is shown in the tables below. We include another set of models in which we add more covariates to the right hand side in another response.

In both of the analyses above, we treat death either as a censoring event, or as progression to account for potential differences in its occurrence across the two patient groups. The significance of the treatment dummy is the same across these two specifications in all but one case.

Please also note that we do not claim that the number of impaired organs is the most important, or sole, indicator of disease progression. However, we do believe it is a measurable indicator that succinctly captures a patient's overall health state and provides a useful way to meaningfully estimate a treatment effect for metreleptin beyond the 15 years of data observed in the NIH Follow-Up study.

- **(B3.b)** Please provide the detailed patient level data from both the NIH Follow-Up study and GL/PL Natural History study, where the type of the afflicted organ as well as the type/severity of each observed organ impairment can be traced.

Response: Data for the Natural History Study and the NIH Follow-Up study are provided. [GL-PL-NaturalHistory.zip and NIH Follow-up Study.zip]

- **(B3.c)** On page 259 of the CS, above Table 71, it is explained that while the patients from the GL/PL Natural History study have data from birth, for patients in the NIH Follow-Up study, data are only available since the start of their treatment. The submission also notes that the resulting truncated data may lead to biased estimates. Please explain the size and the direction of this bias and please justify why no attempt was made to correct for this bias?

Response: Patients with truncated histories are more likely to transition once they are observed than those patients whose prior histories are fully observed. This is because patients with truncated histories are likely to have already spent some time in the state in which they are first observed. Patients whose entire history is observed, on the other hand, spend a longer amount of time in the observed state before transitioning even if they transition at the same rate. This implies that we would estimate higher transition probabilities for those patients with truncated data (NIH patients) than those with full data (GL/PL patients).

For example, suppose that transitions are governed by an exponential decay model, which is the assumption we make when we estimate transition probabilities.[2] Under this assumption, transition to the next state depends only on the length of time a patient spends in the current state. If we observe a group of patients who had already spent some time with impairment to

[2] In such a model, the number of patients who are yet to transition at time *t* is simply the following: $N(t)=N(0)*exp(-\lambda*t)$, where $N(0)$ is the number of patients who just transitioned into the current state.

one organ, but whose histories we do not observe, we essentially treat them as if they have newly developed this impairment at the time they are observed.

It is clear to see that making this assumption would result in larger estimates of the transition probability than would be the case had we observed precisely when these patients develop their first organ impairment. This introduces an upward bias in our estimates of the transition probabilities for NIH patients (whose data is truncated). However, since these are the patients who benefit from the treatment under study, such a bias would make it less likely that we find a beneficial effect of the treatment. Since the bias is against the argument we seek to make in the CS, we note that our claims about the effectiveness of the treatment are conservative.

It is also important to note that the difference in observation period is not the only, or even the main, way in with the NIH Follow-Up study and the Natural History study differ. Partial lipodystrophy (PL) patients in the Natural History study were selected on the basis of medical diagnoses as reported by treating physicians during the observation period (i.e., acquired partial lipodystrophy or familial partial lipodystrophy). There was no distinction made between "severe" PL and "non-severe" PL. This created a group of patients which, as a whole, was likely less severe than PL patients at whom metreleptin treatment is targeted.

- To support this assumption, an exploratory analysis was conducted whereby PL patients from the Natural History study for whom triglycerides (TG) and/or HbA1c lab values were available at any point during the observation period were dichotomized into two subgroups of patients: one "severe" PL group (high HbA1c [≥6.5%] or high TG [≥500 mg/dL]) and one "non-severe" PL group (low HbA1c [<6.5%%] and low TG [<500 mg/dL]).
    - Patients in the severe PL group had a higher mean number of damaged organs during the observation period than patients in the non-severe PL group (2.0 vs. 0.9, Wilcoxon rank-sum test: $p<0.001$).
    - The same trend was observed when a cut-off value of 8.0% was applied for HbA1c (2.1 vs. 1.1, Wilcoxon rank-sum test: $p<0.001$).
- Therefore, using the Natural History study as a comparator group against whom metreleptin-treated patients are compared is most likely a conservative approach.

- **(B3.d)** Please explain how to interpret the steep decline in the KM curves near t=0 in all sub-figures depicted in Figure 35, page 257 of the CS. It suggests that once a patient is being observed, 20% of patients immediately develop an organ failure, regardless of how many organs were already damaged.

Response: Since information about organ abnormalities is collected when patients make physician visits, we sometimes observe that patients are diagnosed with abnormalities to multiple organs at the same date. We deal with these cases by staggering the diagnoses so that they are one day apart. The result is that some patients seem to spend only one day in an abnormality state before transitioning to the next.

For example, a patient who is diagnosed with abnormalities to 2 additional organs, after having previously developed an abnormality to another organ will appear to have spent one day with two organ abnormalities.

The following data summarize instances in which patients in our studies are diagnosed with abnormalities to multiple organs on the same date, as reflected on the transition curves included in our original submission:

- 18 natural history patients develop abnormalities to two organs after having had no prior abnormalities
- 12 natural history patients and 1 NIH patient develop abnormalities to two organs when they already have one afflicted organ
- 10 natural history patients and 1 NIH patient develop abnormalities to two organs when they already have two other afflicted organs
- 4 natural history patients and 2 NIH patients develop abnormalities to 3 organs after having had no prior abnormalities
- 2 natural history patients and 1 NIH patient develop abnormalities to 3 organs when they have previously had one afflicted organ
- 1 natural history patient develops abnormalities to all four organs at the same time

- **(B3.e)** Please justify the plausibility of the assumptions below by conducting formal statistical tests (e.g. t-test, F-test, etc.) on the available patient level data (eligible patients from the NIH Follow-Up study and GL/PL natural history study):
    - **(B3.e.1)** the probability distribution for the total number of impaired organs would follow Markov memoryless property (e.g. transition from one state to another does not depend on the time spent in the former state)

Response: We test for supporting evidence of this assumption using a linear regression framework (results presented below). We run this analysis only within our matched control cohort only as the NIH (treated) patients are observed only after starting treatment and thus a similar test on these patients would not allow us to separately identify the impact of time spent in the former state from effects of treatment by metreleptin. We do not find strong evidence that there is a consistent, significant correlation between time spent in the former state and time to progression for the matched control patients from the Natural History study (untreated).

We believe that the type of Markov process we assume above is a reasonable assumption for the purposes of the CE model. As the goal of the matching criteria is to create a control cohort that imitates the path of the NIH patients absent treatment, we argue that conditional on our matching criteria, it is unlikely that our treated patients from the NIH cohort and their matched controls from the Natural History study differ significantly in time spent in the former state for any number of impaired organs with abnormalities. Although we cannot directly test for supporting evidence of this assumption as we are unable to observe time spent in the former state for the treated NIH patients, our matching criteria (which includes age at start of treatment) balances the two cohorts in an attempt to correct for these potential systematic differences.

Table 8: Markov Assumption Justification Analyses

	Time to Progression		
	2nd Organ	3rd Organ	4th Organ
Time Spent in Previous State	0.033 (0.041)	0.120 (0.087)	0.321 (0.196)
Constant	1,644.938*** (332.601)	942.842*** (245.915)	1,990.180*** (468.392)

Statistical output are shown below:

Linear regression: Time to transition(days) from 3rd to 4th organ impairment on time to transition from 2nd to 3rd impairment (time_to_third_n).

```
Coefficients:
     Estimate Std. Error t value Pr(>|t|)
(Intercept)  1990.1804 468.3919 4.249 0.000173 ***
time_to_third_n -0.3205  0.1964 -1.632 0.112507
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1991 on 32 degrees of freedom
Multiple R-squared: 0.07683,     Adjusted R-squared: 0.04798
F-statistic: 2.663 on 1 and 32 DF, p-value: 0.1125
```

Linear regression: Time to transition (days) from 2nd to 3rd organ impairment on time to transition from 1st to 2nd impairment (time_to_third_n).

```
Coefficients:
     Estimate Std. Error t value Pr(>|t|)
(Intercept)  942.84175 245.91542 3.834 0.000245 ***
time_to_second_n 0.11964 0.08727 1.371 0.174105
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1513 on 83 degrees of freedom
Multiple R-squared: 0.02214,     Adjusted R-squared: 0.01036
F-statistic: 1.879 on 1 and 83 DF, p-value: 0.1741
```

Linear regression: Time to transition (days) from 1st to 2nd organ impairment on time to transition from 0 to 1st impairments (time_to_third_n).

```
Coefficients:
     Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.645e+03 3.326e+02 4.946 2.83e-06 ***
time_to_first_n 3.269e-02 4.094e-02 0.798 0.426
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 2005 on 107 degrees of freedom
Multiple R-squared: 0.005923,    Adjusted R-squared: -0.003367
F-statistic: 0.6376 on 1 and 107 DF, p-value: 0.4264
```

- **(B3.e.2)** probability of developing two or more organ abnormalities in a year or improvement of the existing organ abnormalities would be always zero

Response: Although we do observe patients developing multiple organ abnormalities in a given year (approximately 64% of patients have multiple organ progressions within 1 year), we believe the assumption that only one progression can happen in a cycle is justifiable for the purposes of the CE model. This simplifying assumption would result in a conservative estimate of the benefit of metreleptin treatment. As we find that metreleptin slows organ abnormality progression, the restriction that only one organ can develop abnormalities in one cycle would underestimate the benefit of the drug as this restriction may also slow organ progression of Natural History study (control) patients.

The simplifying assumption that the probability of developing two or more organ abnormalities in a year or improvement of the existing organ abnormality is always zero allows for tractability of the CE Model.

- **(B3.e.3)** the patient characteristics such as age, gender, type of lipodystrophy, type of organ damage and severity of the abnormality, time on metreleptin treatment, blood triglyceride levels have no impact on the transition probabilities for the number of impaired organs.

Response: We acknowledge that these characteristics are important contributors to survival and progression. However, as the goal of our matching criteria is to balance several of these attributes across the NIH (treated) patients and Natural History study (control) patients, we do not anticipate that estimates derived transition probabilities used in the the CE model would be biased by systematic differences in these attributes across groups.

To more directly examine the effect of the mentioned covariates, the NIH Follow-Up data and the matched Natural History data were poole and used in Cox models relating each transition to a indicator flagging whether a patient has been treated or not (treated), an indicator flagging whether a patient has generalised lipodystrophy or partial lipodystrophy (gl), the age at which the patient first experiences symptoms (first_symptom_age), flag indicating whether the patients' pancreas was impaired when they were first observed (Pancreas), flag indicating whether the patients' heart was impaired when they were first observed (Heart), flag indicating whether the patients' liver was impaired when they were first observed (Liver), flag indicating whether the patient's kidney was impaired when they were first observed (Kidney), the patient's baseline blood triglyceride level (num_bsl_tryglycerides). (Please note that the older version of the NIH organ abnormality data was used in these regressions). The the identity of organs impaired at baseline is significant for some organs and some transitions, no consistent pattern emerges.

<u>Transition to 1 organ abnormality from 0 damaged organs</u>
Excluding Triglycerides as a covariate

```
 n= 40, number of events= 40
   (2 observations deleted due to missingness)

                     coef exp(coef) se(coef)      z Pr(>|z|)
treated           0.66687   1.94814  1.13596  0.587    0.557
gl                0.80935   2.24645  0.53999  1.499    0.134
male             -0.22843   0.79578  0.50649 -0.451    0.652
first_symptom_age 0.02655   1.02691  0.02688  0.988    0.323
Pancreas0         0.04262   1.04354  0.42477  0.100    0.920
Heart1            0.07710   1.08016  0.45309  0.170    0.865
```

```
Liver0            -0.51562   0.59713  0.38326 -1.345    0.179
Kidney0           -0.39270   0.67523  0.50320 -0.780    0.435

Concordance= 0.59  (se = 0.059 )
Rsquare= 0.093   (max possible= 0.996 )
Likelihood ratio test= 3.91  on 8 df,   p=0.865
Wald test            = 3.7  on 8 df,   p=0.8831
Score (logrank) test = 3.77  on 8 df,   p=0.8774
```

Including Triglycerides as a covariate

```
n= 11, number of events= 11
   (31 observations deleted due to missingness)

                           coef  exp(coef)   se(coef)      z Pr(>|z|)
treated               -3.030e+01  6.931e-14  3.937e+04 -0.001    0.999
gl                     2.322e+01  1.213e+10  1.337e+04  0.002    0.999
male                   3.139e+01  4.309e+13  3.937e+04  0.001    0.999
first_symptom_age     -1.573e-01  8.545e-01  1.262e-01 -1.247    0.213
Pancreas0             -3.063e+00  4.676e-02  2.283e+00 -1.341    0.180
Heart1                -1.697e+01  4.286e-08  3.937e+04  0.000    1.000
Liver0                -4.618e+01  8.815e-21  4.158e+04 -0.001    0.999
Kidney0               -3.740e+00  2.375e-02  3.890e+00 -0.961    0.336
num_bsl_triglycerides -1.199e-02  9.881e-01  7.313e-03 -1.640    0.101

Concordance= 0.923  (se = 0.131 )
Rsquare= 0.855   (max possible= 0.959 )
Likelihood ratio test= 21.25  on 9 df,   p=0.01159
Wald test            = 2.87  on 9 df,   p=0.9691
Score (logrank) test = 17.99  on 9 df,   p=0.03528
```

Transition to 2 organ abnormality from 1 damaged organ

Excluding Triglycerides as a covariate

```
n= 54, number of events= 46
   (9 observations deleted due to missingness)

                     coef exp(coef) se(coef)      z Pr(>|z|)
treated           0.99645   2.70865  0.80669  1.235  0.21674
gl                1.62816   5.09449  0.53585  3.038  0.00238 **
male              0.20680   1.22974  0.42058  0.492  0.62294
first_symptom_age 0.07319   1.07594  0.02252  3.251  0.00115 **
Pancreas0        -1.21177   0.29767  0.39783 -3.046  0.00232 **
Heart1            1.06351   2.89652  0.42321  2.513  0.01197 *
Liver0            0.22015   1.24626  0.39950  0.551  0.58159
Kidney0          -0.78282   0.45712  0.43114 -1.816  0.06942 .

Concordance= 0.764  (se = 0.055 )
Rsquare= 0.416   (max possible= 0.994 )
Likelihood ratio test= 29  on 8 df,   p=0.0003165
Wald test            = 24.1  on 8 df,   p=0.002201
Score (logrank) test = 27.08  on 8 df,   p=0.0006846
```

Including Triglycerides as a covariate

```
n= 20, number of events= 16
   (43 observations deleted due to missingness)

                           coef  exp(coef)   se(coef)      z Pr(>|z|)
treated               -3.295726   0.037041   2.164861 -1.522  0.12792
gl                     4.941673 140.004325   2.219045  2.227  0.02595 *
male                  -1.246207   0.287594   1.274880 -0.978  0.32832
```

```
first_symptom_age       0.033371   1.033934   0.055349  0.603  0.54657
Pancreas0              -5.189958   0.005572   1.948354 -2.664  0.00773 **
Heart1                  1.917161   6.801623   2.057833  0.932  0.35152
Liver0                 -1.536458   0.215142   1.156221 -1.329  0.18389
Kidney0                 2.199536   9.020823   1.641672  1.340  0.18031
num_bsl_triglycerides  -0.005511   0.994504   0.002217 -2.486  0.01293 *

Concordance= 0.893  (se = 0.095 )
Rsquare= 0.663   (max possible= 0.96 )
Likelihood ratio test= 21.75  on 9 df,   p=0.009716
Wald test            = 8.23  on 9 df,   p=0.5109
Score (logrank) test = 10.81  on 9 df,   p=0.2889
```

Transition to 3 organ abnormality from 2 damaged organs

Excluding Triglycerides as a covariate

```
  n= 77, number of events= 49
   (20 observations deleted due to missingness)
                    coef exp(coef) se(coef)      z Pr(>|z|)
treated          -1.05154   0.34940  0.54771 -1.920   0.0549 .
gl                0.69819   2.01012  0.41339  1.689   0.0912 .
male              0.08914   1.09323  0.39018  0.228   0.8193
first_symptom_age 0.01295   1.01303  0.01456  0.889   0.3738
Pancreas0         0.01714   1.01729  0.38261  0.045   0.9643
Heart1            0.15656   1.16948  0.38798  0.404   0.6866
Liver0           -0.88841   0.41131  0.41612 -2.135   0.0328 *
Kidney0           0.19112   1.21060  0.39558  0.483   0.6290

Concordance= 0.662  (se = 0.048 )
Rsquare= 0.128   (max possible= 0.989 )
Likelihood ratio test= 10.55  on 8 df,   p=0.2286
Wald test            = 10.89  on 8 df,   p=0.208
Score (logrank) test = 11.16  on 8 df,   p=0.193
```

Including Triglycerides as a covariate

```
  n= 46, number of events= 25
   (51 observations deleted due to missingness)

                           coef  exp(coef)   se(coef)      z Pr(>|z|)
treated               -0.9012393  0.4060661  0.8716328 -1.034    0.301
gl                     0.7702729  2.1603558  0.6796773  1.133    0.257
male                  -0.2203722  0.8022201  0.6648777 -0.331    0.740
first_symptom_age      0.0186617  1.0188370  0.0264924  0.704    0.481
Pancreas0              0.3542187  1.4250667  0.6650925  0.533    0.594
Heart1                -0.3387380  0.7126692  0.7849431 -0.432    0.666
Liver0                -0.5359488  0.5851139  0.8021645 -0.668    0.504
Kidney0                0.3069661  1.3592950  0.6447628  0.476    0.634
num_bsl_triglycerides -0.0004979  0.9995023  0.0004630 -1.075    0.282

Concordance= 0.64  (se = 0.069 )
Rsquare= 0.114   (max possible= 0.961 )
Likelihood ratio test= 5.56  on 9 df,   p=0.7827
Wald test            = 5  on 9 df,   p=0.8346
Score (logrank) test = 5.52  on 9 df,
p=0.7871
```

Transition to 4 organ abnormality from 3 damaged organs

Excluding Triglycerides as a covariate

```
n= 78, number of events= 22
   (10 observations deleted due to missingness)
```

```
                     coef exp(coef) se(coef)      z Pr(>|z|)
treated           1.02676   2.79199  0.75333  1.363  0.17290
gl               -0.34605   0.70747  0.65891 -0.525  0.59945
male              0.56944   1.76728  0.62666  0.909  0.36351
first_symptom_age 0.01032   1.01037  0.02351  0.439  0.66063
Pancreas0        -0.35965   0.69792  0.54716 -0.657  0.51099
Heart1           -0.37750   0.68557  0.54488 -0.693  0.48843
Liver0            2.21156   9.12994  0.76079  2.907  0.00365 **
Kidney0          -0.59660   0.55068  0.63094 -0.946  0.34437

Concordance= 0.755  (se = 0.077 )
Rsquare= 0.171   (max possible= 0.851 )
Likelihood ratio test= 14.65  on 8 df,   p=0.06641
Wald test            = 15.3  on 8 df,   p=0.05359
Score (logrank) test = 18.65  on 8 df,   p=0.01685
```

Including Triglycerides as a covariate

```
n= 53, number of events= 10
   (35 observations deleted due to missingness)

                           coef  exp(coef)   se(coef)      z Pr(>|z|)
treated                1.904e+01  1.849e+08  1.245e+04  0.002   0.9988
gl                    -9.862e-01  3.730e-01  9.785e-01 -1.008   0.3135
male                   1.023e+00  2.781e+00  1.037e+00  0.986   0.3242
first_symptom_age     -1.031e-01  9.021e-01  5.479e-02 -1.881   0.0600 .
Pancreas0             -6.400e-01  5.273e-01  1.029e+00 -0.622   0.5340
Heart1                -2.767e+00  6.282e-02  1.487e+00 -1.861   0.0627 .
Liver0                 2.166e+01  2.554e+09  1.245e+04  0.002   0.9986
Kidney0                9.077e-01  2.479e+00  1.512e+00  0.600   0.5482
num_bsl_triglycerides -4.431e-05  1.000e+00  2.155e-04 -0.206   0.8370

Concordance= 0.895  (se = 0.104 )
Rsquare= 0.364   (max possible= 0.735 )
Likelihood ratio test= 24.02  on 9 df,   p=0.004269
Wald test            = 14.67  on 9 df,   p=0.1005
Score (logrank) test = 28.74  on 9 df,   p=0.000717
```

- **(B3.f)** If possible, please provide a de-novo statistical analysis for the estimation and the extrapolation of organ abnormality progression, using common, published methods for transition probability estimation (e.g. multi-state models or maximum likelihood estimates: https://www.ncbi.nlm.nih.gov/pubmed/11788980 https://cran.r-project.org/web/packages/msm/vignettes/msm-manual.pdf), using the pooled dataset (including label-eligible patients from both NIH Follow-Up study as well as the Natural History study) [e.g. multi-state models or maximum likelihood (The statistical analysis should include all relevant covariates , where the relevance of the covariates can be determined based on properly conducted formal statistical tests, as required in the previous bullet point. Please implement the disease progression probabilities derived from this de-novo statistical analysis to the model.

Response: We would be happy to re-implement our approach using the MSM package, but having looked carefully at this request unfortunately this would not be possible for us to

provide by March 2nd. Such a reimplementation could be provided by March 9th, but we await feedback from NICE as to whether this would be acceptable.

B4:

a) Please provide scenarios, in which the attributes like hyperphagia, ability to work, reproduction, physical appearance and fast disease progression do not stay at their baseline values but may change over time.

Response: We are incorporating this functionality into the version of the model that will be provided on March 2nd

b) In the CS, neuropathy, amputation and retinopathy were named in the list of attributes used in the electronic model, which characterised an individual patient's health (first paragraph of section 12.1.6 of the submission). However, in the electronic model, the ERG were unable to find these attributes. Please confirm that these attributes were not actually included in the model as separate attributes and explain the reason for that.

Response: These attributes were not included in the cost-effectiveness model. Our apologies for the error in 12.1.6. While these attributes were included in the discrete choice experiment (and thus utility decrements estimated), data about these attributes was not systematically available in the NIH Follow-Up study and thus they could not been included in the model.

c) Please indicate how "ability to work" was operationalised in the model. For example, explain whether the probability of being partially employed and unemployed, as well as being retired, were taken into consideration.

Response: The impact of the ability to work is only on a patient's utility in the model, and no cost offset or other indirect societal benefit is factored in. For simplicity and since the focus was on change with metreleptin (vs. a comprehensive description of the burden of lipodystrophy e.g. prior to metreleptin use), a patient's ability to work was only characterized as a binary variable e.g. employed vs. not. This was validated with the clinical experts from Addenbrookes when the DCE was designed. With an average follow-up of nearly 5 years, and over ten years for some patients, the change in status post metreleptin was assumed to be sustained over time. While an exogenous probability of retirement could have been imposed (along with a high utility level e.g. sourced from the literature), it seemed inappropriate as it would amount to assuming that with an exogenous probability that lipodystrophy patients get better, which doesn't appear to be consistent with the course of the disease.
The ability to work attribute is operationalized in the same fashion as hyperphagia, diminished reproductive function, impaired physical appearance, and fast progression. Patients observed in the NIH trial data to suffer impaired ability to work are assigned a per-year utility decrement of -.25 but are not assigned any additional annual costs.

B5. Please explain the improved attribute values used for metreleptin (hyperphagia, ability to work, reproduction, physical appearance and fast disease progression) in detail and provide scenarios where the baseline and follow-up attribute values are the same in both metreleptin and SoC arms.

Response: A scenario in which attribute values are the same among MET and SOC patients can be operationalized by setting all non-organ progression and lab value utility decrements to 0. Under this constraint, the model returns a QALY/ICER estimate of 4.1046/£617,174 for the label population.

B6. The "Progression Speed" attribute has an impact on QoL and cost calculations but it has no influence on the disease progression probabilities in the model. Could you please explain how progression speed is measured and the rationale for its impact on QoL and cost calculations without having any impact on disease progression probabilities? If this attribute is related to the speed of disease progression, then please incorporate a scenario where the disease progression probabilities are also affected by this attribute.

Response: The Progression Speed characteristic does not affect the process of organ abnormality progression after the end of the observed data and is included to illustrate the disutility associated with living with an aggressive and progressive disease. Patients are categorized as experiencing fast progression at baseline if they developed more than 1 organ abnormality per 9 years of age prior to metreleptin initiation. Patients are categorized as continuing to experience fast progression after metreleptin initiation if the next organ abnormality is observed within 3 years of metreleptin initiation.

B7. **Priority Question:** Please justify why only a "last observed carried forward" approach was followed in the extrapolation of glucose and triglyceride levels. Please explore other methods for blood glucose (e.g. regression imputation or assuming a linear increase in HbA1c as in other type-2 diabetes models (http://www.core-diabetes.com/)) and triglyceride (e.g. mean imputation) extrapolation. Also, please present a comparison of these attribute values used in the economic model with the values presented in the clinical effectiveness section.

Response: While the NIH Follow-Up study suggests improvements in HbA1c and triglyceride (TG) occur due to metreleptin treatment, there is variation in how much each patient responds and there is variation in laboratory readings over time. Rather than assuming a specific trend for each patient, we chose the LOCF approach to be conservative. Data from our Natural History study also suggests that HbA1c values for untreated patients vary over time, but do not suggest a specific trend. We chose not to use type 2 diabetes models to simulate blood glucose levels in lipodystrophy patients, as lipodystrophy is a distinct clinical condition with a distinct mechanism for elevation of blood glucose. As the costs and utility decrements associated with HbA1c and TG are already included in model sensitivity analyses, the model does reflect some of the potential uncertainty around these values. We will add some functionality to systematically vary HbA1c and TG values over time in the version of the model delivered on March 2.

In addition, the real-world data collected on longer term outcomes including organ abnormalities and mortality allow the CE model to utilize direct burden measures rather than metabolic markers alone.

Please note that the NIH Follow-Up study (used for the CE model) included the same patients as in the clinical trial (discussed in the clinical effectiveness section). The NIH Follow-Up study includes all of the HbA1c and TG reading collected as part of the clinical trial. However, the data were averaged for each patient to reflect the CE model period length of one year Specifically, period 1 values in the CE model reflect readings from 6 months

after metreleptin initiation to 18 months after, period 2 values reflect the average of all readings from 18 months to 30 months, and so on.

Survival analysis

B8. Priority Question: In the company's model, the 'percentage of people alive' at the end of the time horizon is considerably higher than zero (e.g. average probability of being alive at the end of the time horizon is 26.7% in the metreleptin arm). Please provide a scenario with a long time horizon, where the average percentage of people being alive at the end is almost zero. Note that it might require some reprogramming of the model, so that it accommodates longer time horizons than 60 years (maximum).

Response: We are in the process of implementing a longer horizon scenario, and this will be available by March 2.

B9. **Priority Question:** The ERG considers that some of the survival estimates in the submission may lack face validity. For instance, in the model, PL patients who have a lower number of impaired organs compared to the baseline average of the NIH Follow-Up study, have a better life expectancy than the UK general population.

- Please confirm that mortality estimates for PL/GL patients should not be below the national lifetable age/sex specific values. Please provide alternate clinically plausible mortality estimates (which cannot be lower than the UK general mortality figures, even if the patient has no organ abnormality). Please implement these estimates in the model.

Response: We can confirm that we would not expect PL/GL patients to have higher survival rates (lower mortality) than the general UK population, and we have implemented this cap in the model (SIM_ALIVE_CAPPED). Upon implementation, we find it has nearly no impact on QALY/ICER estimates for key population groups.

- For the mortality of GL patients, data from the NIH Follow-Up was used (CS page 259). For the extrapolation of that data the approach as outlined by Latimer was followed, but it appears that a crucial step was not included, i.e. checking the clinical plausibility of the extrapolated part of the curve. Hence, please provide external data or expert opinion to assess if another parametric function than the exponential should be used in the base case.

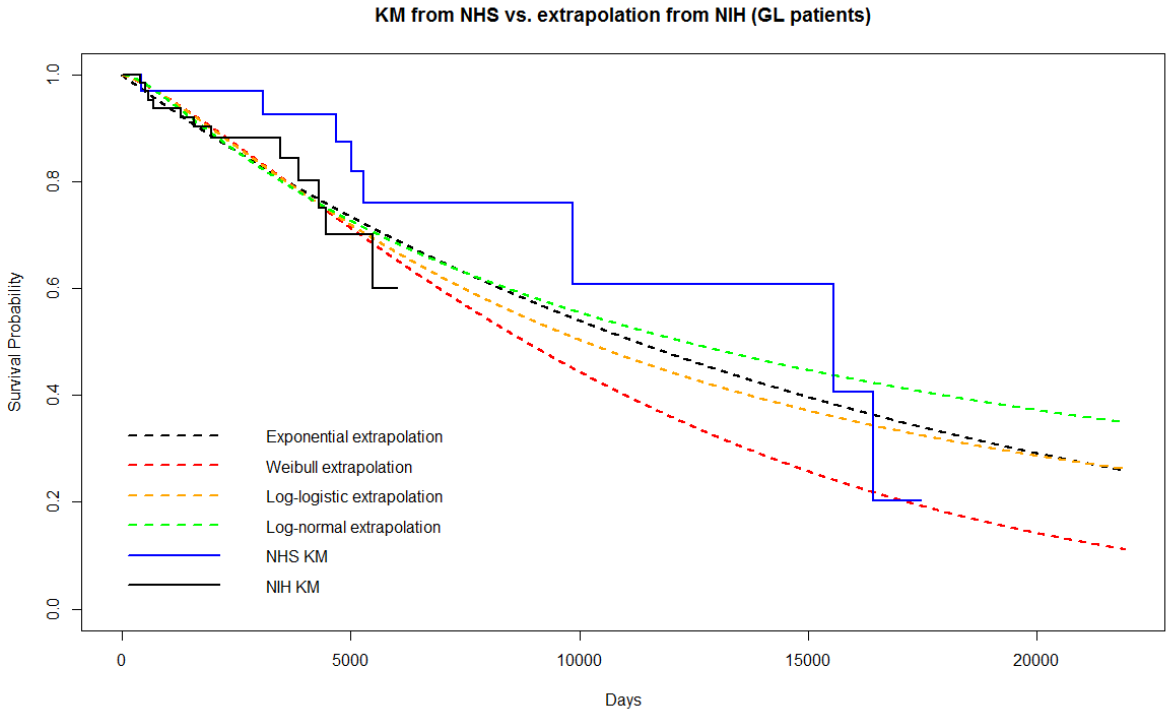
Response: In order to check the clinical plausibility of the extrapolated portion of the curve, we use data from the Natural History Study on GL patients whose age profile matches that of patients in the NIH study. This is the only external data we have access to, since the condition we study is so rare and, to the best of our knowledge, no longitudinal other patient data on mortality is available. More specifically, to compare the survival extrapolation to the observed survival in the Natural History study, we exclude from the Natural History study any patients whose end of observation is prior to the average starting age of the NIH GL patient cohort (17.55 years). We then advance the remaining patients in the Natural History study until they reach age 17.55 years such that none of the survival time before age 17.55 years is counted, and plot the KM curve setting the time at which they reach this age threshold to 0 (e.g., index date).

We effectively match the two groups of GL patients on average age at the start of the NIH trial and observe their mortality outcomes moving forward. The graph in Figure 1 shows that the exponential extrapolation is in line with this constructed KM curve from the Natural History study. Note that lipodystrophy among the patient population in the Natural History study is (on average) less advanced than among the NIH population (see section Matching Methodology section, on page 271 in the CS for more details), thus we would expect the Natural History study KM curve to be, on average, above the NIH study KM curve.

Despite the differences in the underlying patient population, the long duration of observation for some natural history patients provides some information about the long term survival prospects of patients with GL. The extrapolated curves from the NIH study continue to be below the observed KM curve for the Natural History study for most of the period observed in natural history patients, but the rate of mortality and overall shape seem consistent.

Please note that the last known date of survival for patients in the NIH Follow-Up was extended from January 2017 to December 2017 after the original survival extrapolation was conducted, and Figure 1 below reflects the original data used for the extrapolation. Data input files and code for this extrapolation validation exercise is provided [B9_GL-Survival-Extrapolation-Validation.zip]

Figure 1: Extrapolation validation for GL patients



B10: Priority Question: Please answer the queries related to the survival analyses below:

- **(B10.a)** The survival study explained in Appendix 6 includes an extrapolation exercise (17.6.2.2) for the survival of the GL/PL patients using parametric models and national life tables, followed by an estimation exercise (17.6.2.3) for the relationship between organ abnormality and mortality. While the extrapolation

exercise was conducted on the patients from the NIH Follow-Up study, the estimation exercise was conducted on the patients from the GL/PL Natural History study. The hazard ratio coefficient from the estimation exercise is applied to the parametric/life table survival curves obtained from the extrapolation exercise. Please explain why the natural history dataset is used for the estimation exercise instead of NIH Follow-Up dataset.

Response: The estimation of the relationship between organ impairment and mortality was conducted using only the Natural History study because of the data limitations of the NIH study. Since we only observe patients at the start of the trial in the NIH data, we lack information about the early stage of their disease. Moreover, the observation window in the trial is much shorter than that in the GL/PL study. A Cox proportional hazards model on the NIH study did not yield any significant results, as shown in Table 9 below. Therefore, we did not estimate the effect of organ impairment on mortality using the NIH study, and only used the Natural History study for the estimation exercise.[3]

Table 9: Cox Proportional Hazards Model of mortality on number of impaired organs using data from the NIH Study

Independent Variable	Cox Coefficient (Beta)	Exponential of Cox Coefficient (Hazard Ratio)	Standard Error (coefficient)	p-value	R2	Likelihood ratio test
FULL SAMPLE						
Number of Impaired Organs (n=112)	0.4658	1.5933	0.3249	0.152	0.011	1.98 P = 0.1599
GL SAMPLE						
Number of Impaired Organs (n=68)	0.3768	1.4576	0.3420	0.271	0.011	1.17 P = 0.28
PL SAMPLE						
Number of Impaired Organs (n=44)	1.525	4.593	1.254	0.224	0.024	1.67 P = 0.1968

Full statistical outputs for the NIH study are shown below.
Cox model on full sample with 112 patients:

```
N(intervals)= 178, number of events= 13
```

[3] One of our patients in the Natural History Study (Encrypted Patient ID: 53605772) suffered kidney impairment at birth. For this particular patient, we assumed no kidney damage in our initial analysis of the effect of organ impairment on mortality. We have since changed our approach to take this patient's impairment into account in all new analyses involving the Natural History dataset. The resulting estimate of the coefficient on organ abnormality in our Cox model is almost identical to the original estimate, hence our results are not sensitive to this change.

```
    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 0.4658 1.5933 0.3249 1.434 0.152

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  1.593  0.6276 0.8428  3.012

Concordance= 0.677 (se = 0.099 )
Rsquare= 0.011 (max possible= 0.409 )
Likelihood ratio test= 1.98 on 1 df, p=0.1599
Wald test   = 2.06 on 1 df, p=0.1516
Score (logrank) test = 2.11 on 1 df, p=0.1461
```

Cox model on GL sample with 68 patients:

```
 N(intervals)= 109, number of events= 12

    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 0.3768 1.4576 0.3420 1.102 0.271

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  1.458  0.686 0.7457  2.849

Concordance= 0.662 (se = 0.086 )
Rsquare= 0.011 (max possible= 0.548 )
Likelihood ratio test= 1.17 on 1 df, p=0.28
Wald test   = 1.21 on 1 df, p=0.2705
Score (logrank) test = 1.24 on 1 df, p=0.2662
```

Cox model on PL sample with 44 patients:

```
 N(intervals)= 69, number of events= 1

   coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.525  4.593 1.254 1.216 0.224

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  4.593  0.2177 0.3936  53.6

Concordance= 0.878 (se = 0.278 )
Rsquare= 0.024 (max possible= 0.1 )
Likelihood ratio test= 1.67 on 1 df, p=0.1968
Wald test   = 1.48 on 1 df, p=0.2239
Score (logrank) test = 1.81 on 1 df, p=0.1779
```

Data input files and code for the statistical analyses performed using the latest data[4] is provided [B10_CoxSurvivalModel_NIHStudy.zip]

- **(B10.b)** Also provide de-novo extrapolation and estimation exercises, using data from a pooled dataset including label-eligible patients from both NIH Follow-Up and Natural History studies, incorporating the study ID as a separate covariate. Please implement the findings of this de-novo analysis to the model.

Response: We ran a time varying cox proportional hazard model relating mortality to number of organs with abnormalities (as well as additional covariates) on pooled data, as requested. We first created a pooled dataset with all NIH patients along with matched natural history patients ("matched data set") based on the Mahalanobis matching method using the latest available data[4]. The second method of pooling combines all NIH and all Natural

[4] After our submission to NICE in January, data for the NIH Study was updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed

History patients ("pooled data set"). Our baseline model includes covariates such as GL/PL type, an indicator for study ID (as requested), gender, and age at the start of follow-up. We also ran a number of models to test the sensitivity of our estimates by including other covariates. The resulting estimates in these models were similar in size to those we obtained in our main specification. See the accompanying code for details of those models, which can be readily replicated.

For the matched dataset, the updated coefficients on organ abnormality result in an ICER of £657,769, and the corresponding QALY gain is 8.31. For the pooled data set, the resulting ICER is £661,544, and the corresponding QALY gain is 8.29. This is for the label population, when we apply 0% discount. We also estimate survival curves using the pooled dataset and implement these in the ISM model as a new base case.

Data input files and code for the statistical analyses performed using the latest available data[5] are provided [B10_CoxSurvivalModel_Pooled.zip]

Below, we report the full statistical output from the Cox models for both the matched and pooled data sets:

MATCHED DATASET

Matched dataset - Cox model on full sample with 166 patients, including number of organs with abnormalities (sum_organs), an indicator for PL (glplPL), an indicator for being in the NIH Follow-Up study (study_idNIH), and indicator for female (gender1), and the patients age at the start of observation (age_at_start, 0 for most Natural History patients, and age at metreleptin initiation for NIH Follow-Up patients) :

```
  N= 335(intervals), number of events= 23

                   coef  exp(coef)   se(coef)      z Pr(>|z|)
sum_organs    8.984e-01  2.456e+00  2.386e-01  3.765 0.000166 ***
glplPL       -1.974e+00  1.389e-01  6.765e-01 -2.918 0.003522 **
study_idNIH   1.889e+01  1.601e+08  7.084e+03  0.003 0.997872
gender1      -8.542e-02  9.181e-01  5.236e-01 -0.163 0.870410
age_at_start  3.221e-02  1.033e+00  2.193e-02  1.469 0.141865
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
sum_organs   2.456e+00  4.072e-01   1.53846     3.920
glplPL       1.389e-01  7.200e+00   0.03688     0.523
study_idNIH  1.601e+08  6.246e-09   0.00000       Inf
gender1      9.181e-01  1.089e+00   0.32903     2.562
age_at_start 1.033e+00  9.683e-01   0.98929     1.078

Concordance= 0.868  (se = 0.076 )
Rsquare= 0.124   (max possible= 0.408 )
Likelihood ratio test= 44.37  on 5 df,   p=1.947e-08
Wald test            = 20.88  on 5 df,   p=0.0008551
Score (logrank) test = 40.73  on 5 df,   p=1.064e-07
```

to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017.

[5] After our submission to NICE in January, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017.

Matched dataset - Cox model on GL sample with 97 patients:

```
  N(intervals)= 190, number of events= 18

                   coef  exp(coef)   se(coef)      z Pr(>|z|)
sum_organs    6.890e-01  1.992e+00  2.584e-01  2.666  0.00767 **
study_idNIH   1.875e+01  1.396e+08  7.514e+03  0.002  0.99801
gender1      -3.956e-02  9.612e-01  5.699e-01 -0.069  0.94466
age_at_start  4.920e-02  1.050e+00  2.254e-02  2.183  0.02905 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
sum_organs   1.992e+00  5.021e-01    1.2003     3.305
study_idNIH  1.396e+08  7.163e-09    0.0000       Inf
gender1      9.612e-01  1.040e+00    0.3146     2.937
age_at_start 1.050e+00  9.520e-01    1.0050     1.098

Concordance= 0.812  (se = 0.083 )
Rsquare= 0.124   (max possible= 0.482 )
Likelihood ratio test= 25.2  on 4 df,   p=4.591e-05
Wald test            = 10.45  on 4 df,   p=0.03354
Score (logrank) test = 26.29  on 4 df,   p=2.762e-05
```

Matched data set - Cox model on PL sample with 69 patients:

```
  N(intervals)= 145, number of events= 5

                   coef  exp(coef)   se(coef)      z Pr(>|z|)
sum_organs    1.912e+00  6.767e+00  8.923e-01  2.143   0.0321 *
study_idNIH   1.931e+01  2.437e+08  2.035e+04  0.001   0.9992
gender1      -2.291e+00  1.012e-01  2.133e+00 -1.074   0.2827
age_at_start -6.517e-02  9.369e-01  6.612e-02 -0.986   0.3243
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
sum_organs   6.767e+00  1.478e-01  1.177275    38.894
study_idNIH  2.437e+08  4.103e-09  0.000000       Inf
gender1      1.012e-01  9.885e+00  0.001548     6.611
age_at_start 9.369e-01  1.067e+00  0.823020     1.067

Concordance= 0.911  (se = 0.197 )
Rsquare= 0.074   (max possible= 0.146 )
Likelihood ratio test= 11.19  on 4 df,   p=0.02456
Wald test            = 5.04  on 4 df,   p=0.2834
Score (logrank) test = 12.51  on 4 df,   p=0.01394
```

POOLED DATASET

Pooled dataset - Cox model on full sample with 290 patients, including number of organs with abnormalities (sum_organs), an indicator for PL (glplPL), an indicator for being in the NIH Follow-Up study (study_idNIH), and indicator for female (gender1), and the patients age at the start of observation (age_at_start, 0 for most Natural History patients, and age at metreleptin initiation for NIH Follow-Up patients) :

```
N(intervals)= 592, number of events= 27

     coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 9.335e-01 2.543e+00 2.030e-01 4.598 4.27e-06 ***
glplPL  -2.163e+00 1.150e-01 5.762e-01 -3.753 0.000175 ***
study_idNIH 1.959e+01 3.217e+08 6.693e+03 0.003 0.997665
gender1  4.439e-01 1.559e+00 4.468e-01 0.993 0.320534
age_at_start 3.604e-02 1.037e+00 2.110e-02 1.708 0.087720 .
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

    exp(coef) exp(-coef) lower .95 upper .95
```

```
sum_organs 2.543e+00 3.932e-01 1.70839 3.7866
glplPL  1.150e-01 8.693e+00 0.03718 0.3559
study_idNIH 3.217e+08 3.108e-09 0.00000  Inf
gender1  1.559e+00 6.416e-01 0.64927 3.7420
age_at_start 1.037e+00 9.646e-01 0.99469 1.0805

Concordance= 0.928 (se = 0.065 )
Rsquare= 0.131 (max possible= 0.338 )
Likelihood ratio test= 83.22 on 5 df, p=2.22e-16
Wald test   = 40.28 on 5 df, p=1.311e-07
Score (logrank) test = 105.5 on 5 df, p=0
```

Cox model on GL sample with 124 patients including number of organs with abnormalities (sum_organs), an indicator for being in the NIH Follow-Up study (study_idNIH), and indicator for female (gender1), and the patients age at the start of observation (age_at_start, 0 for most Natural History patients, and age at metreleptin initiation for NIH Follow-Up patients):

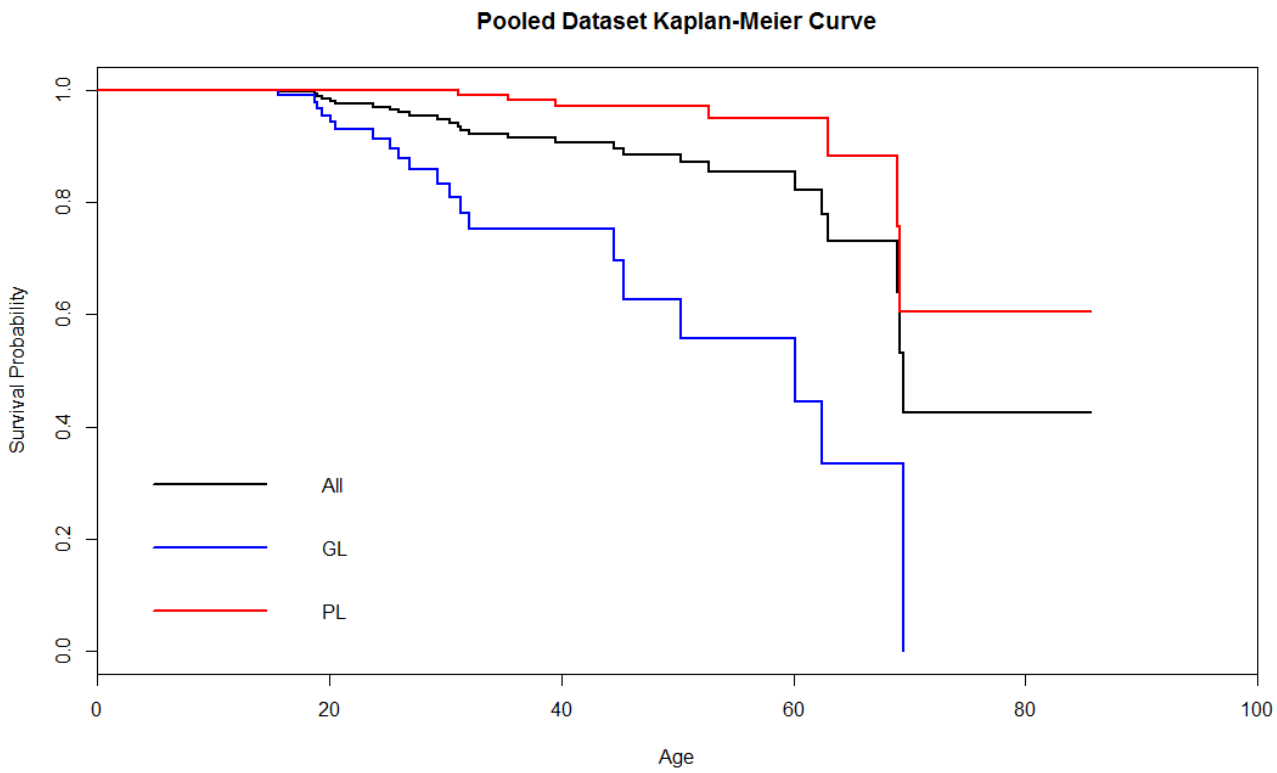
```
N(intervals)= 244, number of events= 20

     coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 7.947e-01 2.214e+00 2.467e-01 3.221 0.00128 **
study_idNIH 1.913e+01 2.027e+08 6.389e+03 0.003 0.99761
gender1  5.589e-01 1.749e+00 5.018e-01 1.114 0.26538
age_at_start 5.182e-02 1.053e+00 2.232e-02 2.321 0.02028 *
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

    exp(coef) exp(-coef) lower .95 upper .95
sum_organs 2.214e+00 4.517e-01  1.365  3.590
study_idNIH 2.027e+08 4.933e-09  0.000  Inf
gender1  1.749e+00 5.718e-01  0.654  4.676
age_at_start 1.053e+00 9.495e-01  1.008  1.100

Concordance= 0.853 (se = 0.08 )
Rsquare= 0.135 (max possible= 0.447 )
Likelihood ratio test= 35.52 on 4 df, p=3.633e-07
Wald test   = 14.01 on 4 df, p=0.007263
Score (logrank) test = 40.71 on 4 df, p=3.08e-08
```

Cox model on PL sample with 166 patients including number of organs with abnormalities (sum_organs), an indicator for being in the NIH Follow-Up study (study_idNIH), and indicator for female (gender1), and the patients age at the start of observation (age_at_start, 0 for most Natural History patients, and age at metreleptin initiation for NIH Follow-Up patients):

```
N(intervals)= 348, number of events= 7

     coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.657e+00 5.246e+00 5.264e-01 3.149 0.00164 **
study_idNIH 1.914e+01 2.058e+08 1.295e+04 0.001 0.99882
gender1  -9.233e-01 3.972e-01 9.784e-01 -0.944 0.34532
age_at_start -5.747e-02 9.442e-01 6.672e-02 -0.861 0.38904
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

    exp(coef) exp(-coef) lower .95 upper .95
sum_organs 5.246e+00 1.906e-01 1.86970 14.720
study_idNIH 2.058e+08 4.859e-09 0.00000  Inf
gender1  3.972e-01 2.518e+00 0.05838  2.703
age_at_start 9.441e-01 1.059e+00 0.82841  1.076

Concordance= 0.942 (se = 0.146 )
Rsquare= 0.051 (max possible= 0.12 )
Likelihood ratio test= 18.12 on 4 df, p=0.00117
Wald test   = 10.32 on 4 df, p=0.0354
Score (logrank) test = 25.08 on 4 df, p=4.853e-05
```

Below is the KM curve (by GL/PL status) for the pooled dataset, as requested. Data input files and code is provided [B10_PooledKMCurves.zip]

Figure 2: Pooled data KM Curves



- **(B10.c)** The results in Table 75 (page 266) suggests that the number of impaired organs is a significant covariate, but the ERG question if it is the only one, noting that p-values alone might not be the only decision criteria to decide on which covariates to include. Please provide all relevant details (dataset used, statistical codes compiled as well as the whole statistical outputs from the analyses including R^2 and goodness of fit results) for the survival analysis exercises conducted (base case and those in Table 75) with their explanations and provide other prognostic survival models with additional covariates (for example type of the disease, treatment received and any other relevant covariates), on the natural history dataset, NIH Follow-Up study dataset and the pooled dataset, including only label-eligible patients.

Response: In response to this request, we have estimated Cox models with additional covariates and presented the results below.

Datasets and codes for the Cox models using the Natural History Study with the original data have been provided [B10_CoxSurvivalModel_NaturalHistory.zip].
Statistical outputs for each Cox model are shown below.

Baseline model – full sample with 178 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 414, number of events= 14

    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.2839 3.6108 0.3329 3.857 0.000115 ***
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

```
   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  3.611  0.2769  1.88  6.934

Concordance= 0.882 (se = 0.12 )
Rsquare= 0.05 (max possible= 0.157 )
Likelihood ratio test= 21.22 on 1 df, p=4.099e-06
Wald test   = 14.88 on 1 df, p=0.0001149
Score (logrank) test = 26.48 on 1 df, p=2.668e-07
```

Baseline model –GL sample with 56 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 135, number of events= 8

    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.0897 2.9734 0.4155 2.623 0.00873 **
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  2.973  0.3363  1.317  6.713

Concordance= 0.843 (se = 0.117 )
Rsquare= 0.069 (max possible= 0.237 )
Likelihood ratio test= 9.61 on 1 df, p=0.001935
Wald test   = 6.88 on 1 df, p=0.008725
Score (logrank) test = 11.42 on 1 df, p=0.0007247
```

Baseline model–PL sample with 122 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 279, number of events= 6

    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.5237 4.5892 0.5302 2.874 0.00406 **
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  4.589  0.2179  1.623  12.97

Concordance= 0.904 (se = 0.121 )
Rsquare= 0.042 (max possible= 0.116 )
Likelihood ratio test= 12.03 on 1 df, p=0.0005229
Wald test   = 8.26 on 1 df, p=0.004055
Score (logrank) test = 17.14 on 1 df, p=3.475e-05
```

Model sensitivity 1 on full sample with 178 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 414, number of events= 14

     coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs  3.93667 51.24774 3.68263 1.069 0.285
sum_organs_sq -0.38949 0.67740 2.01964 -0.193 0.847
sum_organs_cub -0.06185 0.94002 0.34090 -0.181 0.856

    exp(coef) exp(-coef) lower .95 upper .95
sum_organs  51.2477 0.01951 0.03758 69877.662
sum_organs_sq  0.6774 1.47623 0.01293 35.479
sum_organs_cub 0.9400 1.06381 0.48190  1.834

Concordance= 0.946 (se = 0.065 )
Rsquare= 0.101 (max possible= 0.218 )
Likelihood ratio test= 43.89 on 3 df, p=1.592e-09
Wald test   = 16.07 on 3 df, p=0.001097
Score (logrank) test = 62.73 on 3 df, p=1.532e-13
```

Model sensitivity 2 on full sample with 178 patients, including number of organs with abnormalities (sum_organs), age, indicator for female (gender1), and country (country1) :

```
 n(intervals)= 414, number of events= 14

     coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.7035861 5.4936126 0.3846092 4.429 9.45e-06 ***
age   0.0004888 1.0004890 0.0228490 0.021 0.983
gender1  0.1937144 1.2137496 0.6550882 0.296 0.767
country1 -0.5334388 0.5865843 0.6808295 -0.784 0.433
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs 5.4936  0.1820 2.5851 11.674
age   1.0005  0.9995 0.9567  1.046
gender1  1.2137  0.8239 0.3361  4.383
country1  0.5866  1.7048 0.1545  2.228

Concordance= 0.944 (se = 0.097 )
Rsquare= 0.091 (max possible= 0.218 )
Likelihood ratio test= 39.36 on 4 df, p=5.873e-08
Wald test   = 28.89 on 4 df, p=8.242e-06
Score (logrank) test = 60 on 4 df, p=2.908e-12
```

Model sensitivity 3 on full sample with 178 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, and leptin:

```
 n(intervals)= 414, number of events= 14

       coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs    1.873749 6.512670 0.363060 5.161 2.46e-07 ***
num_bsl_hemoglobin_a1c -0.261286 0.770061 0.432365 -0.604 0.546
num_bsl_triglycerides -0.001798 0.998204 0.001810 -0.993 0.321
num_bsl_leptin   -0.232359 0.792661 0.246952 -0.941 0.347
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    6.5127  0.1535 3.1968 13.268
num_bsl_hemoglobin_a1c 0.7701  1.2986 0.3300  1.797
num_bsl_triglycerides  0.9982  1.0018 0.9947  1.002
num_bsl_leptin   0.7927  1.2616 0.4885  1.286

Concordance= 0.941 (se = 0.091 )
Rsquare= 0.099 (max possible= 0.218 )
Likelihood ratio test= 43.09 on 4 df, p=9.9e-09
Wald test   = 28.05 on 4 df, p=1.216e-05
Score (logrank) test = 61.39 on 4 df, p=1.482e-12
```

Model sensitivity 4 on full sample with 178 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, leptin, age, indicator for female (gender1), and indicatory for country (country1):

```
 n(intervals)= 414, number of events= 14

       coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs    2.017188 7.517155 0.465604 4.332 1.47e-05 ***
num_bsl_hemoglobin_a1c -0.168343 0.845064 0.493977 -0.341 0.733
num_bsl_triglycerides -0.002167 0.997835 0.001836 -1.180 0.238
num_bsl_leptin   -0.266450 0.766094 0.266053 -1.001 0.317
age     -0.004775 0.995236 0.025004 -0.191 0.849
gender1     0.350113 1.419228 0.686823 0.510 0.610
country1    -0.742169 0.476080 0.765326 -0.970 0.332
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    7.5172  0.1330 3.0181 18.723
num_bsl_hemoglobin_a1c 0.8451  1.1833 0.3209  2.225
num_bsl_triglycerides  0.9978  1.0022 0.9943  1.001
num_bsl_leptin   0.7661  1.3053 0.4548  1.290
age      0.9952  1.0048 0.9476  1.045
gender1     1.4192  0.7046 0.3693  5.454
country1     0.4761  2.1005 0.1062  2.134
```

```
Concordance= 0.955 (se = 0.097 )
Rsquare= 0.101 (max possible= 0.218 )
Likelihood ratio test= 44.18 on 7 df, p=1.972e-07
Wald test   = 25.91 on 7 df, p=0.0005224
Score (logrank) test = 63.3 on 7 df, p=3.296e-11
```

Model sensitivity 4 on GL sample with 56 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, leptin, age, indicator for female (gender1), and indicatory for country (country1):

```
 n(intervals)= 135, number of events= 8

       coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs    1.871142 6.495709 0.823224 2.273 0.0230 *
num_bsl_hemoglobin_a1c -0.264345 0.767709 1.560951 -0.169 0.8655
num_bsl_triglycerides -0.006280 0.993739 0.005714 -1.099 0.2717
num_bsl_leptin    NA  NA 0.000000  NA  NA
age     -0.029539 0.970893 0.061317 -0.482 0.6300
gender1     2.327878 10.256154 1.292819 1.801 0.0718 .
country1    -3.117316 0.044276 1.659819 -1.878 0.0604 .
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    6.49571  0.1539 1.293890 32.610
num_bsl_hemoglobin_a1c 0.76771  1.3026 0.036017 16.364
num_bsl_triglycerides 0.99374  1.0063 0.982673  1.005
num_bsl_leptin    NA   NA  NA  NA
age      0.97089  1.0300 0.860950  1.095
gender1     10.25615  0.0975 0.813833 129.251
country1     0.04428 22.5857 0.001711  1.146

Concordance= 0.924 (se = 0.134 )
Rsquare= 0.117 (max possible= 0.237 )
Likelihood ratio test= 16.83 on 6 df, p=0.009948
Wald test   = 7.23 on 6 df, p=0.3005
Score (logrank) test = 15.13 on 6 df, p=0.0193
```

Model sensitivity 4 on PL sample with 122 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, leptin, age, indicator for female (gender1), and indicatory for country (country1):

```
 n(intervals)= 279, number of events= 6

        coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs    2.1243346 8.3673280 0.8921632 2.381 0.0173 *
num_bsl_hemoglobin_a1c -0.5219081 0.5933872 0.7628192 -0.684 0.4939
num_bsl_triglycerides -0.0002665 0.9997335 0.0029271 -0.091 0.9275
num_bsl_leptin   -0.2794411 0.7562062 0.3537236 -0.790 0.4295
age      0.0044091 1.0044188 0.0432232 0.102 0.9188
gender1    -0.7081594 0.4925499 1.1823639 -0.599 0.5492
country1    -0.6376429 0.5285368 1.8004896 -0.354 0.7232
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    8.3673  0.1195 1.45605 48.084
num_bsl_hemoglobin_a1c 0.5934  1.6852 0.13305  2.646
num_bsl_triglycerides  0.9997  1.0003 0.99401  1.005
num_bsl_leptin   0.7562  1.3224 0.37805  1.513
age      1.0044  0.9956 0.92283  1.093
gender1     0.4925  2.0303 0.04853  4.999
country1     0.5285  1.8920 0.01551 18.016

Concordance= 0.915 (se = 0.162 )
Rsquare= 0.058 (max possible= 0.116 )
Likelihood ratio test= 16.77 on 7 df, p=0.01896
Wald test   = 8.67 on 7 df, p=0.2772
Score (logrank) test = 21.29 on 7 df, p=0.003367
```

(B10.d) In the model, it is not clear why the UK life table is referred to in the end of each formula in the "SIM_Alive" sheet (from column M and onwards). Please explain.

Response: The UK life table (general population survival curve) is used for PL patients when the PL mortality benefit is switched off in the "Survival Assumptions" input tab.

- **(B10.e)** Please explain why the age of the patient is taken as an index for the PL patients survival calculations, whereas for GL patients, this index is the time from the start of the treatment?

Response: Patients with PL did not appear to experience a substantial reduction in mortality relative to the general public, on average, in the Natural History study. The UK life tables were thus used for the basis of our PL survival modelling included in the cost-effectiveness model, with increased hazard of mortality applied for PL patients with greater than average levels of organ damage. As patients with PL typically started metreleptin at later ages and thus age-related mortality becomes a relevant driver in later periods of the CE model, we chose to use age-specific mortality. For GL patients, the basis for the survival curves in the model is the treated population in the NIH Follow-Up study. Observation of these patients begins when treatment starts, and thus KM curves and survival extrapolations were conducted using the treatment start date as the index value. As GL patients experience substantial premature mortality due to their disease, and as GL patients were typically quite young when beginning treatment, disease-specific mortality (as mediated by metreleptin treatment) was chosen to drive modelled survival.

Matching:

B11. Priority Question: (B11a) Please provide all further details (datasets used, statistical codes compiled as well as the outputs of the statistical analysis) of the matching exercise in 17.6.2.4 with their explanations. Please confirm whether these analyses are in line with the NICE DSU TSD 17.

Response: Input data and code using the original methods and original data presented in 17.6.2.4 are provided [B11_Matching_OriginalData.zip]. Input data and code using the original methods and latest data available[6] are provided as well [B11_Matching_NewData.zip].

Explanation of Matching Algorithm

[6] After our submission to NICE in January, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017. Pancreatitis data have also been updated to reflect validation of pancreatitis incidence by an NIH clinician. We also corrected an inconsistency in which heart conditions were considered abnormalities in the NIH data used for this analysis relative to the definition used in the Natural history data and the definition used in the CE model. Specifically, hypertension was included as an abnormality in the previous version of this analysis. The revised data is consistent with the definition of heart abnormality used in the CE model.

Patients in the untreated sample were followed from birth while patients in the treated sample were first observed at the time of treatment. Additionally, two of the centers in the Natural History study also offered metreleptin treatment and appear to have preferentially selected patients with more severe symptoms for treatment. Therefore, the treated patients were, on average, at a more advanced stage of the disease at the start of observation compared to the untreated patients. This makes it difficult to conduct a straightforward comparison of the two groups. In order to create comparable groups of data, a matching algorithm was designed to minimize the differences between the treated patients and untreated patients in terms of age, gender, and the initial number of impaired organs.

To account for the fact that the untreated group was followed from birth while the treated group was followed from the start of treatment, multiple “pseudo-patients” were created from every individual in the untreated group, each with a different starting age. This allowed for a greater set of untreated patients to be matched to each treated patient, and ensured that each individual in matched pairs would be more similar to its respective match at the start of observation.

The matched pairs were determined using the following algorithm:

1.) Subset GL/PL patients in the treated and untreated groups so that patients are only matched GL to GL and PL to PL.

2.) Create pseudo-patients with different starting ages.

    a. So, for example, a patient who died or was censored at age 27 is split into 27 different “pseudo-patients,” with a starting ages of 0, 1, 2 … 24, 25, and 26.

3.) Find the difference (Diff) of each parameter (age, gender, initial number of organs impaired) between each treated patient and every untreated pseudo-patient.

    a. Diff = (Absolute difference between the treated and untreated individuals) / (Standard deviation of the absolute difference between the treated and untreated individuals)

    b. For gender, males were coded to be 1 and females 0.

4.) Match each treated patient without replacement to the untreated pseudo-patient that minimizes an objective function (a weighted average of the differences in age, gender, and initial number of organs impaired).

    a. The objective function took the form:

        α * Diff(Age) + **β** * Diff(Initial Organ Impairment) + (1 - α - β) * Diff(Gender)

        Being able set the weights **α**, **β** allows for a flexible approach where changes to the relative importance of each characteristic for measuring the distance between treated and untreated patients can be made. The weights were set as **α** = 0.35 and **β** = 0.35 in the final version of the analysis.

Robustness Check – Nearest Neighbors Using Mahalanobis Distance

NICE DSU TSD 17 recommends two different matching methods when matching two inexact datasets: propensity score matching and nearest neighbour matching. Our matching algorithm more closely follows the nearest neighbour matching method. As defined in NICE DSU TSD 17, “nearest neighbour matching typically uses a multivariate measure of distance (typically the Mahalanobis distance) to identify matches that are as close as possible to the treated individual.” Our approach of choosing a Natural History Study pseudo-patient who minimizes the objective function is similar to the nearest neighbour matching approach that minimizes the Mahalanobis distance.

Using the MatchIt R package, a new set of matched Natural History Study patients is selected. The MatchIt function takes in the NIH patient and Natural History Study pseudo-patient dataset. It then returns the matched set of Natural History Study pseudo-patients using nearest neighbour matching that minimizes the Mahalanobis distance between matched pairs. As shown below, the summary statistics and transition probabilities between the matched Natural History Study patients selected using our previous matching approach and the matched Natural History Study patients selected using the MatchIt function show similar values. This suggests that the characteristics between the two sets of matched Natural History Study patients are similar. Therefore, we argue that our previous matching approach is in line with NICE DSU TSD 17’s matching methods to estimate treatment effects using non-randomised data.

Matching Analyses and Output

At the time we conducted our matching analysis, we used NIH data on mortality and the incidence of pancreatitis that is now out of date. As such, we are using this opportunity to incorporate the updated data[7] into our analysis, using the new matching methods. The following shows the results of these analyses using our original matching approach compared to the Mahalanobis approach (new matching approach) as well as using both the original and updated data.

The datasets and code of the statistical analysis from the MatchIt matching exercise using the original data are provided [B11_Matching_Mahalanobis_OriginalData.zip]. The datasets and code of the statistical analysis from the MatchIt matching exercise using the latest available data[7] are provided as well [B11_Matching_Mahalanobis_NewData.zip].

There are two updates to the analysis submitted in the CS in January 2018. The first is in response to NICE reviewer comments and relates to the matching method used to create a

[7] After our submission to NICE in January, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017. Pancreatitis data have also been updated to reflect validation of pancreatitis incidence by an NIH clinician. We also corrected an inconsistency in which heart conditions were considered abnormalities in the NIH data used for this analysis relative to the definition used in the Natural history data and the definition used in the CE model. Specifically, hypertension was included as an abnormality in the previous version of this analysis. The revised data is consistent with the definition of heart abnormality used in the CE model.

comparable sample of untreated patients. The second relates to updates made to the data we use for NIH patients. We note that the resulting changes to the QALY gains and ICER estimated for the label eligible population in light of these updates is negligible. Using the previously submitted data along with our original matching method, the ICER-QALY pair we estimate is (£661,567, 8.29), while using the submitted data with the new matching method yields (£660,488, 8.31). Using the updated data with the original matching method yields an ICER-QALY pair of (£661,687, 8.29), while applying the new matching method to the updated data yields (£658, 487, 8.33). These numbers reflect recent changes made to the ISM, including capped survival, and a new hazard ratio estimated from the pooled data.

Comparison of Nearest Neighbour Matching with Mahalanobis Distance to the Previous Matching Approach using the original data

Below are the outputs sample statistics, KM curves, and transition probabilities using both the original approach and the MatchIt Mahalanobis approach. Both approaches leverage the original dataset (non-updated data). Results for the original approach appear in Section 17.6.2.4 (Tables 77 and 78, and figure 42 and 43) and some of these results are replicated here for convenience.

Table 10: Sample statistics of treated and matched untreated pseudo-patients: Initial approach to Mahalanobis approach

	Treated (NIH)	**Untreated (matched Natural History study patients using previous matching approach)**	**Untreated (matched Natural History study patients using Mahalanobis)**
Age at first symptoms (mean)	13.33	13.94	14.88
Age at start of treatment (mean)	24.28	25.51	25.89
Number of impaired organs at start of treatment (mean)	2.52	2.36	2.38
Number of mortality events (count)	13	31	31
% male	16.96	16.96	16.96

Figure 3: Cumulative survival KM curves for NIH study and matched Pseudo patients using Mahalanobis matching

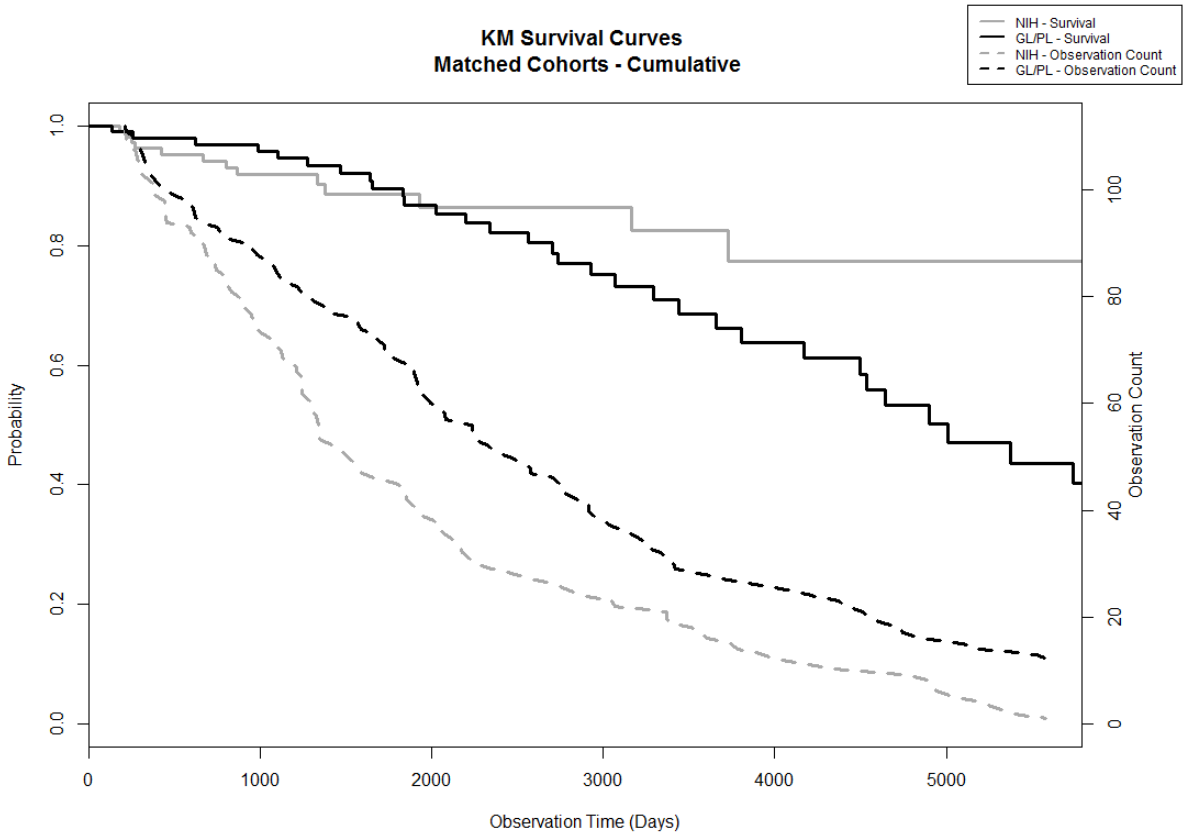


Figure 4: Organ abnormality progression among matched natural history patients based on patients selected using Mahalanobis matching

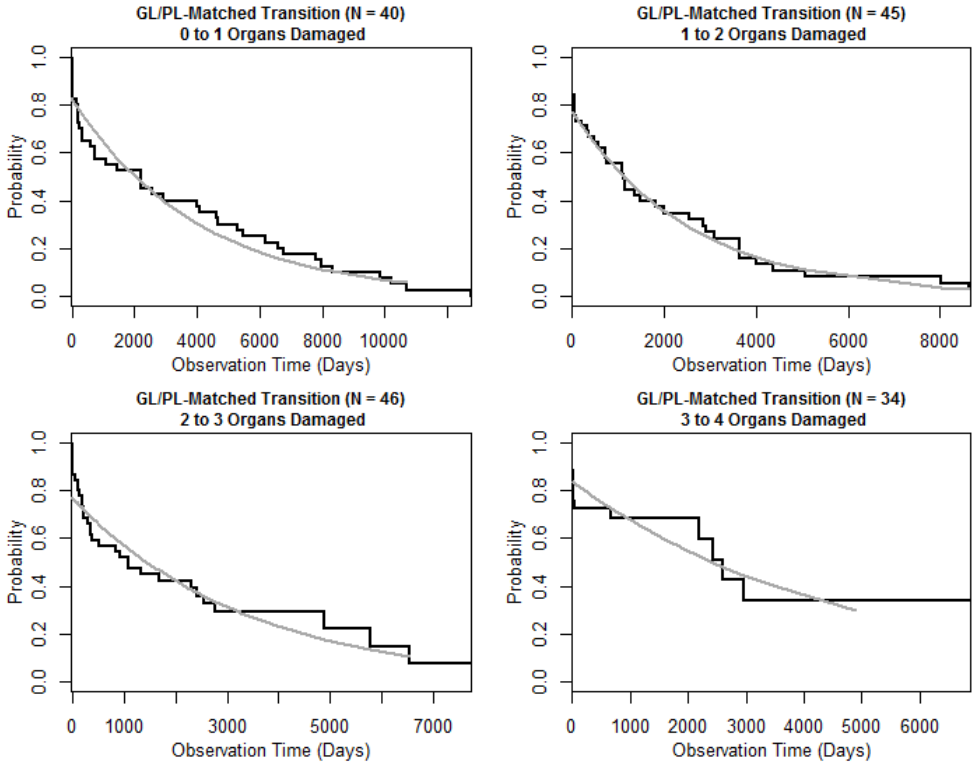


Table 11: Estimated progression probabilities - NIH Patients (using Mahalanobis matching)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	5.37%	4	1
1 to 2	5.00%	13	5
2 to 3	8.33%	47	17
3 to 4	3.91%	48	7

Table 12: Estimated progression probabilities - Matched Natural History Patients (using original matching approach)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	8.9%	36	36
1 to 2	17.3%	42	39
2 to 3	12.3%	44	36
3 to 4	6.2%	36	16

Table 13: Estimated progression probabilities - Matched Natural History Patients (using Mahalanobis matching)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	8.7%	40	40
1 to 2	13.2%	45	42
2 to 3	10.4%	46	33
3 to 4	7.4%	34	15

Outputs with Nearest Neighbour Matching and the Mahalanobis Distance using updated data

Below are the outputs using Matchit (Mahalanobis approach) and the updated data[8]. The results are similar to those generated using the original data.

Table 14: Sample statistics of treated and matched untreated pseudo-patients

	Treated (NIH)	Untreated (matched Natural History study patients using MatchIt and original data)	Untreated (matched Natural History study patients using MatchIt and updated data)
Age at first symptoms (mean)	13.33	14.88	14.69
Age at start of treatment (mean)	24.28	25.89	25.26
Number of impaired organs at start of treatment (mean)	2.41	2.38	2.27
Number of mortality events (count)	13	31	31
% male	16.96	16.96	16.96

[8] After our submission to NICE in January, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017. Pancreatitis data have also been updated to reflect validation of pancreatitis incidence by an NIH clinician. We also corrected an inconsistency in which heart conditions were considered abnormalities in the NIH data used for this analysis relative to the definition used in the Natural history data and the definition used in the CE model. Specifically, hypertension was included as an abnormality in the previous version of this analysis. The revised data is consistent with the definition of heart abnormality used in the CE model.

Figure 5: Cumulative survival KM curves for NIH study and matched Pseudo patients, Mahalanobis approach with updated data

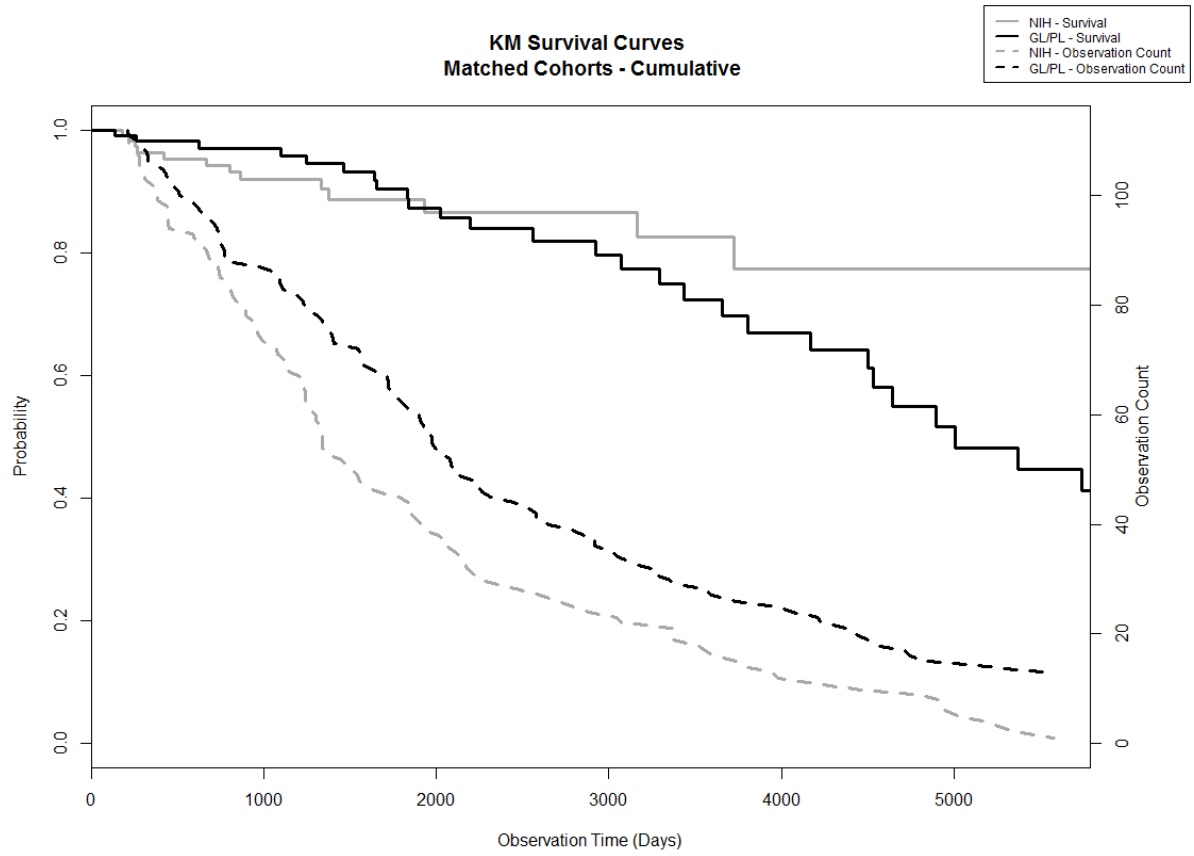


Figure 6: Organ abnormality progression among matched natural history patients based on patients selected with Mahalanobis matching

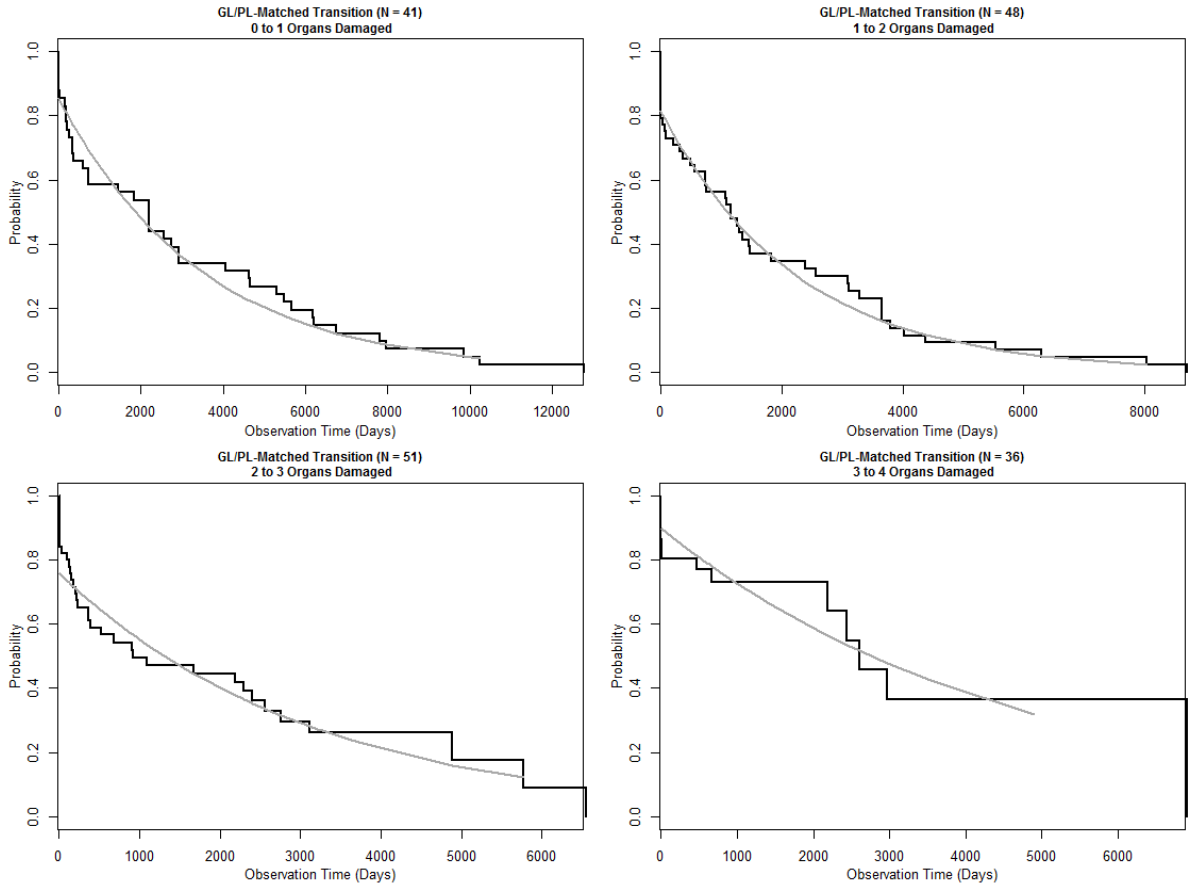


Table 15: Estimated progression probabilities - NIH patients (updated data)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	2.09%	3	1
1 to 2	6.49%	17	7
2 to 3	3.19%	50	17
3 to 4	2.33%	50	5

Table 16: Estimated progression probabilities - Mahalanobis matched patients (updated data)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	10.00%	41	41
1 to 2	14.98%	48	46
2 to 3	10.65%	51	35
3 to 4	7.43%	36	14

Outputs using our previous matching approach and updated data

For reference, below are analysis and outputs generated using our previous matching approach and the updated data[9]. Table 17: Sample statistics of treated and matched untreated pseudo-patients using our previous matching approach

Table 17: Sample statistics of treated and matched untreated pseudo-patients (previous matching approach, updated data)

	Treated (NIH)	**Untreated (matched Natural History study patients using previous matching approach and updated data)**
Age at first symptoms (mean)	13.33	14.27
Age at start of treatment (mean)	24.28	25.17
Number of impaired organs at start of treatment (mean)	2.41	2.28
Number of mortality events (count)	13	31
% male	16.96	16.96

[9] After our submission to NICE in January, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017. Pancreatitis data have also been updated to reflect validation of pancreatitis incidence by an NIH clinician. We also corrected an inconsistency in which heart conditions were considered abnormalities in the NIH data used for this analysis relative to the definition used in the Natural history data and the definition used in the CE model. Specifically, hypertension was included as an abnormality in the previous version of this analysis. The revised data is consistent with the definition of heart abnormality used in the CE model.

Figure 7: Cumulative survival KM curves NIH and matched Pseudo patients (previous matching approach, updated data)

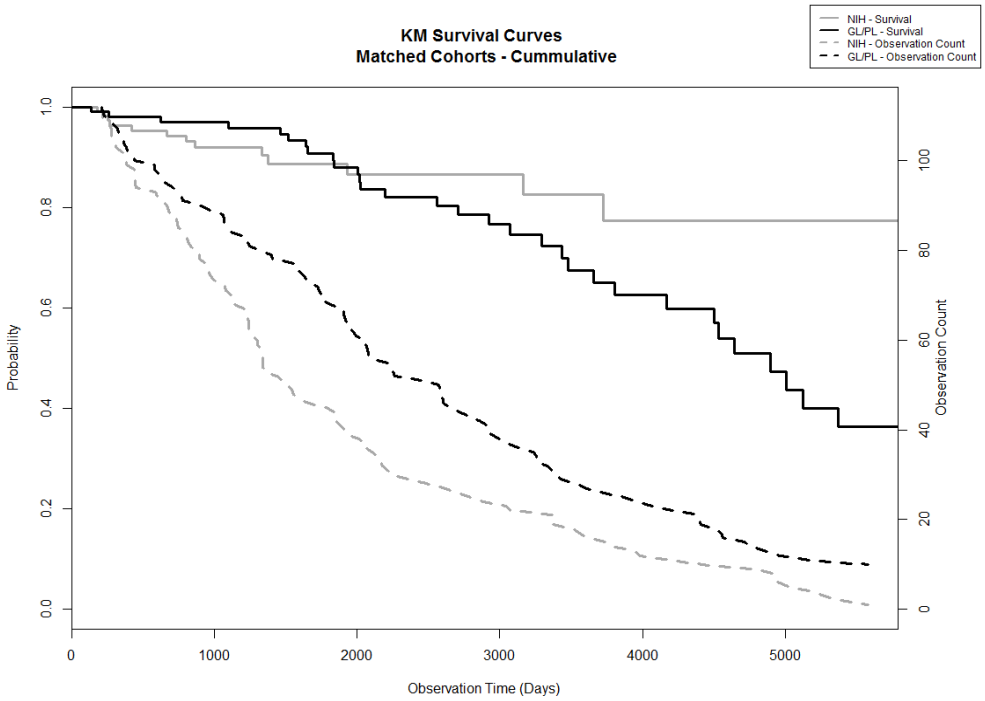


Figure 8: Organ abnormality progression among matched natural history patients (previous matching approach, updated data)

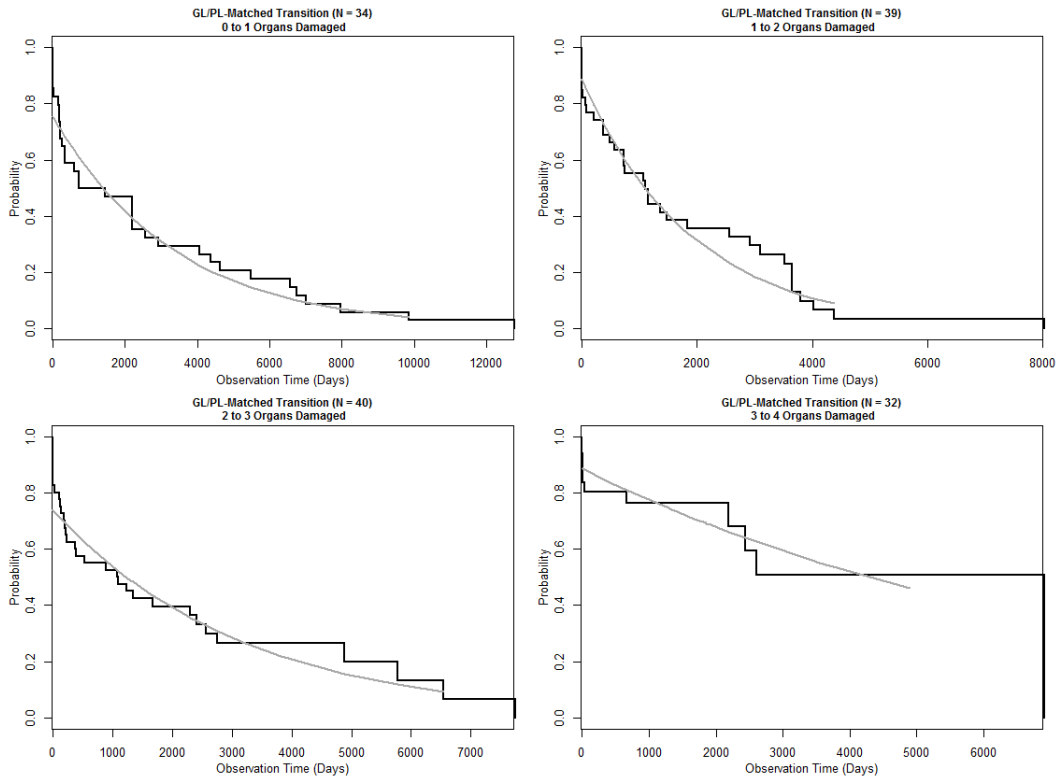


Table 18: Estimated progression probabilities - NIH patients, updated data

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	2.09%	3	1
1 to 2	6.49%	17	7
2 to 3	3.19%	50	17
3 to 4	2.33%	50	5

Table 19: Estimated progression probabilities - matched patients (previous method), updated data

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	10.33%	34	34
1 to 2	17.38%	39	35
2 to 3	10.95%	40	32
3 to 4	4.75%	32	11

- **(B11b)** Please explain why only age, gender and initial organ damage used in the matching.

Response: In selecting the covariates with which to match patients across the NIH Follow-Up and Natural History studies, we sought those variables most likely to characterize a patient's disease progression. Our objective was to create cohorts of patients whose disease was equally severe at the start of observation. Note that we also match on GL/PL status, in addition to age, gender and initial organ abnormality. The NIH study determined the earliest date at which treated patients were observed – the date at which they began treatment with metreleptin. A patient's age and the number of organs with abnormalities they have developed is a coarse but informative measure of their disease progression rate. Gender is a commonly used demographic covariate for which we have data on both groups of patients, and hence is included in the set of variables we use to match on.

- **(B11c)** Please also explain why the matched SoC transition probabilities in Table 78 suggest a faster progression compared to the unmatched SoC transition probabilities in Table 70.

Response: The untreated natural history patients were observed since birth while treated NIH patients were first observed at the time of treatment. Additionally, two centres in the Natural History study also offered metreleptin and appear to have preferentially offered treatment to more symptomatic patients. Therefore, the treated patients were, on average, at a more advanced stage of the disease at the start of observation. As the matched natural history patients were chosen to more closely resemble the NIH patients in terms of severity,

it is not surprising that the matched patients exhibit faster disease progression than the unmatched natural history patients.

B12. It is not clear how the KM plots for SoC were generated in Figure 43 (page 274). No survival analysis results for the patients under SoC were presented in the clinical effectiveness part of the submission (e.g. 6.1.3). Please provide the survival data used and the corresponding KM curves from the natural history PL/GL patients.

Response: The graph in Figure 43 was generated by first matching a natural history pseudo-patient to each NIH patient. All NIH patients are used to create the NIH KM curve, and the list of all matched Natural History Study pseudo-patients is used to create the Natural History Study KM curve. The dashed lines depict the number of patients in the study at each point in time. Data and code to generate this figure is provided [B11_Matching.zip]

Survival data and code used to generate the KM curve for the full, unmatched Natural History Study has also been provided, and the summary report for this study includes KM curves for the full study and for GL and PL subsets. [GL-PL-NaturalHistory.zip]

Utilities:

B13: **Priority Question:**

a) Please provide a detailed explanation for why DCE was chosen as a method to estimate health state utilities, after EQ-5D was deemed to be insufficient.

Explain why the EQ-5D was insufficient

Response Upon review of the literature, appropriate EQ-5D data for LD related symptoms and outcomes in the model were not available (per systematic literature review) nor were robust data covering other generic instruments (e.g., SF-36) which could potentially be mapped to EQ-5D. Likewise, a disease specific HRQoL instrument was not available. In addition, the EQ 5D domains themselves were not considered fully appropriate for lipodystrophy. This is because the domains informing the EQ-5D do not adequately capture the myriad of lipodystrophy related complications and symptoms that impact on the quality-of-life of patients with the condition, and lacks the granularity to understand the individual impact of each complication on the patient. These include specific and distinct disease attributes such as hyperphagia, female reproductive dysfunction, changes in physical appearance, or organ damage. Patient experience and feedback is that each of these influences HRQoL in distinct manner and so an approach that attempts to capture that distinct impact would be most appropriate. While a time trade-off (TTO) study design (as referenced in TSD 12) might also allow for the development of disease-specific utilities, this approach is much less tractable than a discrete choice experiment (DCE) with a heterogeneous disease in which many attributes may be present or absent in individual patients. Hence, it was felt that a DCE would be the most appropriate way to determine the separate impact of the large range of attributes that patients may experience, particularly in the context of a rare and severely debilitating condition reviewed under the HST regime. Aegerion has therefore sponsored the Lipodystrophy Health Utility Survey. In this study a DCE was conducted within the general population to provide the estimates of health disutilities associated with key lipodystrophy attributes from a societal perspective.

The preference for use of the well-validated EQ-5D instrument when available and appropriate is understood. The alternative approach employed in this submission is based on the limited prior research available and clinical opinion regarding the most important disease attributes affecting quality of life of patients with lipodystrophy. The study design aligns with prior research in the field, including Bansback et. al. (2012) to derive robust utility values from the DCE approach.[10] Specifically, the DCE survey presented respondents with choices between two patient scenarios constructed by assigning relevant levels to the defined disease attributes and varying selected attribute values between scenarios. By presenting systematically defined variations in multiple scenario pairs and by including remaining years of life an attribute within each scenario, the utility decrement and time trade-off associated with variation in each individual attribute can be derived. This method of choice elicitation is also considered easier to implement than alternative approaches.[11]

b) Please provide more detailed information regarding the DCE that was done to find disutility estimates pertaining to lipodystrophy disease attributes. This information should provide details regarding the experimental design, explaining for example whether an orthogonal design, a full factorial design or some other experimental design was used.

Response: The online survey included discrete choice questions preceded by a detailed tutorial on attributes and levels. We surveyed 1000 respondents, 250 of whom were in the US, and the remainder were from the EU5 countries (150 each). We opted for a Partial Profile Design with around 23 total attribute levels, 12 of which were visible in the choice cards of each respondent (see section 17.5.2 in the submission document for more details on attribute levels).

The main reason we opted for a Partial Profile Design is that there were too many attribute levels for all to be reasonably included in one choice card. There were 14 choice cards presented to respondents (12 of which were used to infer utilities while 2 were used to test the consistency of responses). Female respondents were exposed to choice cards with information about impairments to female reproductive function, while male respondents were not. Respondents were randomly assigned to one of 12 groups. Within each group, respondents saw an identical set of choice cards.

c) Please also explain the selection process of attributes, given that several of them may be correlated.

[10] "A principle finding from this study is that, in contrast to the [time trade-off] TTO, the inclusion of respondents that may not have understood or engaged with the [DCE], or who were 'irrational' in the task, had little influence on the results." (Bansback et al. (2012), pp. 313)
[11] "Unlike the conventional [time trade-off] TTO, DCEs require respondents to simply indicate that option A is preferred to B, without going through an iterative process of identifying the point at which the respondent is indifferent between A and B. DCE tasks are generally considered simple to complete, and they are often conducted without an interviewer through postal or on-line surveys, but this is dependent on characteristics of the specific task including the number of attributes." (Bansback et al. (2012), pp. 307)

Response: Attributes were selected to cover key symptoms of lipodystrophy and side effects associated with metreleptin treatment in consultation with clinical experts at Addenbrookes, which treats UK lipodystrophy patients today, and at NIH in the US.

Available literature and prior studies:

- Akinci B, Onay H, Demir T, Ozen S, Kayserili H, Akinci G, et al. Natural History of Congenital Generalized Lipodystrophy: A Nationwide Study From Turkey. The Journal of clinical endocrinology and metabolism. 2016;101(7):2759-67
- Brown RJ, Araujo-Vilar D, Cheung PT, Dunger D, Garg A, Jack M, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. The Journal of clinical endocrinology and metabolism. 2016;101(12):4500-11.
- Garg A. Clinical review#: Lipodystrophies: genetic and acquired body fat disorders. The Journal of clinical endocrinology and metabolism. 2011;96(11):3313-25.
- Garg A. Gender differences in the prevalence of metabolic complications in familial partial lipodystrophy (Dunnigan variety). The Journal of clinical endocrinology and metabolism. 2000;85(5):1776-82.
- Gupta N, Asi N, Farah W, Almasri J, Barrionuevo P, Alsawas M, et al. Clinical features and management of non-HIV-related lipodystrophy in children: A systematic review. Journal of Clinical Endocrinology and Metabolism. 2017;102(2):363-74.
- Lima JG, Nobrega LH, de Lima NN, do Nascimento Santos MG, Baracho MF, Jeronimo SM. Clinical and laboratory data of a large series of patients with congenital generalized lipodystrophy. Diabetology & metabolic syndrome. 2016;8:23.
- Misra A, Garg A. Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. Medicine. 2003;82(2):129-46.
- Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, et al. Leptin-replacement therapy for lipodystrophy. New England Journal of Medicine. 2002;346(8):570-8.
- Oral EA, Ruiz E, Andewelt A, Sebring N, Wagner AJ, Depaoli AM, et al. Effect of leptin replacement on pituitary hormone regulation in patients with severe lipodystrophy. The Journal of clinical endocrinology and metabolism. 2002;87(7):3110-7.
- Musso C, Cochran E, Javor E, Young J, DePaoli AM, Gorden P. The long-term effect of recombinant methionyl human leptin therapy on hyperandrogenism and menstrual function in female and pituitary function in male and female hypoleptinemic lipodystrophic patients. Metabolism: clinical and experimental. 2005;54(2):255-63.
- Lupsa BC, Sachdev V, Lungu AO, Rosing DR, Gorden P. Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. Medicine. 2010;89(4):245-50.

d) Please, also include all details of the statistical models (datasets used, statistical codes compiled as well as the outputs of the statistical analysis) that have been explored in 17.5.2.5, in order to estimate the utility values, incorporating the detailed output of the analyses.

Response: The underlying dataset and code has been provided [B13_METAnalyses_UtilityEstimation.zip]

B14: Priority Question: The ERG notes that additive approach followed in the submission of applying attribute disutilities in QALY derivation often leads to negative values for total QALYs (see for example the number of QALYs for SoC in Table D49). This would imply that on average, patients receiving SoC would rather be dead than living with lipodystrophy. Also, one of the two references in the CS, Ara and Brazier 2012 suggests using the multiplicative approach together with a range of sensitivity analyses. Note that the other reference, Viney et al. 2014, also shows preference for a model with interaction (possibly multiplicative) rather than additive because "interaction terms reflect their preference complementarity, namely, that two or more health problems' combined impact is less than the sum of the individual main effects". This seems reasonable in this setting when multiple attributes define the health status of a patient.

- Please adapt the analysis in 17.5.2.5 to provide disutility estimates that are fit for use in the multiplicative approach.
- Please modify the model such that it accommodates the application of the disutilities in a multiplicative way as an option and present an analysis using the estimates requested in the previous bullet point .

Response:
Regarding the "negative values for total QALYs" in Table D49, we would like to clarify that Table D49 shows the discounted expected QALYs for treated patients and those under the SoC. The negative QALY value for SoC patients is not uncommon for a condition that affects multiple attributes. Note that the EQ-5D-derived preference-based index in the Ara and Brazier (2012) study cited in the question has a range of -0.59 to 1. The negative value of -0.6 in Table D49 pertains to the expected discounted QALYs over the model's 60 years of simulated patient trajectories and must not be interpreted as an annual QALY value.

Regarding the comment that "Ara and Brazier 2012 suggests using a multiplicative approach together with a range of sensitivity analyses", and likewise similar guidance in TSD 12: we have reviewed the referenced work and concluded that the methods discussed are not directly relevant to our analysis of DCE data. In the section below, we summarize Ara and Brazier (2012) and TSD 12 and describe the difference between the objectives of these two studies and the objective of our estimation approach:

- Ara and Brazier (2012) propose five methods to estimate health state utility values (HSUVs) using EQ-5D data from the Health Survey of England: the additive method, the multiplicative method, the minimum method, the adjusted decrement method, and a linear regression. The authors propose four "sensitivity analyses" to compare the performance of these 5 methods: the mean absolute error (MAE), the root mean square error (RMSE), the minimum important difference (MID), and the magnitude

and direction of errors across the EQ-5D range. TSD 12 is similarly focused on the question of calculating appropriate utilities for patients with comorbidities: "[…] we look at the data used to represent the HSUVs for individuals who do not have particular health conditions […], the methods used to combine HSUVs for comorbidities and the methods used to capture uncertainty in HSUVs"[12]. The appendix of TSD 12 contains a list of methods used to estimate HSUVs for comorbidities, which includes the multiplicative method.[13]

- These studies are not concerned with estimating the utilities associated with attribute impairment (as we are), but instead use existing, previously estimated, EQ-5D QALY decrements to impute the quality of life of patients living with multiple comorbid conditions. The challenge these two sources consider is a lack of quality of life data on patients living with, say, two conditions simultaneously when those data are only available for patients living with each of the two conditions separately. Our DCE exercise, on the other hand, has had to address the absence of any QALY data for the diverse attributes of a single condition, lipodystrophy, estimating these quantities from original experimental choice data.
- While use of a multiplicative method may be appropriate when combining EQ-5D QALY decrements for comorbid conditions jointly affecting individual EQ-5D domains, the distinct and previously under researched attributes of lipodystrophy are better suited to the approach we have taken, building on Viney et. al. 2014 (see below).

Question B14 also includes the comment that "[…] the other reference, Viney et al. 2014, also shows preference for a model with interaction (possibly multiplicative) rather than additive." We believe that Viney et al. (2014) actually supports the approach we have taken. Nonetheless, in response to the question, we also estimate models with interaction terms and discuss the impact their estimates are likely to have on our analysis.

- The "multiplicative interaction terms" discussed in Viney et al. (2014) relate to additional terms that may be added to the right hand side of an equation that estimates the disutility associated with impairment to a vector of attributes. Consider the case of patients who only face impairment to two attributes, A and B. An estimation equation that allows for only two parameters, one for each attribute, would yield disutilities for each impairment and stipulate a linear relationship between impairment and utility.
- If, on the other hand, the analyst considers that the disutility associated with simultaneous impairment to both attributes may not be well modelled by simply adding the two decrements, they may choose to add an interaction term to the right hand side of their estimation equation. This term would allow for some non-linearity in the functional relationship between impairment and utility. Note that this relates to an exercise conducted before there are usable utility decrements, and the analyst is faced with a dataset of choices.
- The "multiplicative method" described in Ara and Brazier (2012) and TSD 12 relates to one possible way in which the utility of patients suffering from multiple conditions

[12] TSD 12, page 4

[13] TSD 12, page 28.

(the individual utilities of which are known) can be estimated. Note that this exercise presumes the existence of utilities associated with each condition. As such, the estimation of utility decrements that would have been used to calculate the condition-specific utilities is not the focus of these studies.

- In contrast, Viney et al. (2014) is in fact concerned with the estimation of utility decrements associated with specific conditions, not the evaluation of utility arising from comorbidities.
- We used Viney et al. (2014) as a guide in our econometric analysis and have adopted the simplest version of their model. However, we can also estimate the coefficients associated with interaction terms between different attribute levels:
    - Our original model allows us to estimate coefficients associated with the presence and absence of all attributes of interest, but we omit interaction terms that measure the non-additive effects of disutility from impairment to multiple attributes.
    - We can estimate a model with both main effects (those we already include) and interaction terms, as requested. In Model 2 below, the latter are included only for the most severe attribute levels, similar to Viney et al.'s (2014) approach.
    - In model 3, we include interaction terms among the attributes with the highest main effect decrements.
- Note that most coefficients in model 3 are negative, indicating that respondents perceive that the disutility from having multiple attribute impairments is higher than the sum of the individual disutilities. Importantly, by omitting these terms, our analysis may be underestimating the QALY impact of metreleptin, since treated patients experience a smaller benefit relative to SoC patients. Moreover, since we chose to implement our survey through a partial profile design (see response to question B13), estimates of interaction terms may be subject to bias and should be interpreted with caution.[14]

Finally, while we do not feel that direct inclusion of utility losses associated with each attribute in our DCE in a multiplicative manner is consistent with the literature, we are in the process of adapting the CE to accept such values, and are also directly estimating a multiplicative utility function from the DCE data. We will provide the updated model and these results on March 2.

New sources:

Bryan Orme and Keith Chrzan (2017), "Becoming an Expert in Conjoint Analysis", Sawtooth Software Inc.

Roberta Ara and Allan Wailoo (2011), "NICE DSU Technical Support Document 12: The Use of Health State Utility Values in Decision Models", Report by the Decision Support Unit

[14] "Partial-profile CBC had some of the same weaknesses inherent to other partial-profile approachs (such as ACA): […] Reduced ability to estimate interaction effects compared to full-profile CBC (since each pair of attributes is only present in a subset of choice tasks)." (Orme and Chrzan (2017), page 91)

Table 20: Utility decrement estimation with interactions

		Model 1				Model 2				Model 3		
		Coefficients	Decrements	Significance		Coefficients	Decrements	Significance		Coefficients	Decrements	Significance
Life remaining		0.077	1.000	1.0%		0.077	1.000	1.0%		0.068	1.000	1.0%
Life remaining x Amputation present		-0.021	-0.270	1.0%		-0.020	-0.264	1.0%		-0.013	-0.197	1.0%
Life remaining x Ability to perform work impaired		-0.020	-0.255	1.0%		-0.019	-0.252	1.0%		-0.007	-0.103	1.0%
Life remaining x Chronic pain present		-0.012	-0.153	1.0%		-0.011	-0.145	1.0%		-0.011	-0.165	1.0%
Life remaining x Depression present		-0.013	-0.175	1.0%		-0.014	-0.180	1.0%		-0.005	-0.067	10.0%
Life remaining x Heart damage present		-0.014	-0.187	1.0%		-0.015	-0.189	1.0%		-0.008	-0.113	1.0%
Life remaining x Hyperphagia		-0.009	-0.113	1.0%		-0.008	-0.105	1.0%		-0.009	-0.136	1.0%
Life remaining x Impaired physical appearance present		-0.008	-0.101	1.0%		-0.007	-0.096	1.0%		-0.009	-0.128	1.0%
Life remaining x Impaired blood sugar control at level 2		-0.005	-0.064	1.0%		-0.004	-0.058	1.0%		-0.004	-0.052	1.0%
Life remaining x Impaired blood sugar control at level 3		-0.006	-0.079	1.0%		-0.006	-0.073	1.0%		-0.006	-0.094	1.0%
Life remaining x Impaired blood sugar control at level 4		-0.014	-0.180	1.0%		-0.015	-0.194	1.0%		-0.005	-0.070	5.0%
Life remaining x Kidney damage present		-0.010	-0.128	1.0%		-0.010	-0.129	1.0%		-0.011	-0.160	1.0%
Life remaining x Liver damage present		-0.012	-0.153	1.0%		-0.011	-0.149	1.0%		-0.009	-0.137	1.0%
Life remaining x Loss of response to Treatment present		-0.011	-0.149	1.0%		-0.012	-0.154	1.0%		-0.011	-0.157	1.0%
Life remaining x Lymphoma present		-0.010	-0.132	1.0%		-0.011	-0.141	1.0%		-0.011	-0.159	1.0%
Life remaining x Neuropathy present		-0.012	-0.155	1.0%		-0.012	-0.156	1.0%		-0.014	-0.200	1.0%
Life remaining x Pancreas damage present		-0.010	-0.128	1.0%		-0.010	-0.127	1.0%		-0.012	-0.176	1.0%
Life remaining x Progression of Organ Damage present at level 2		0.002	0.032	5.0%		0.002	0.031	5.0%		0.004	0.055	1.0%
Life remaining x Progression of Organ Damage present at level 3		-0.012	-0.162	1.0%		-0.016	-0.207	1.0%		-0.009	-0.127	1.0%
Life remaining x Retinopathy present		-0.015	-0.189	1.0%		-0.014	-0.187	1.0%		-0.007	-0.109	1.0%
Life remaining x Triglycerides present at level 2		-0.004	-0.048	1.0%		-0.004	-0.046	1.0%		-0.005	-0.071	1.0%
Life remaining x Triglycerides present at level 3		-0.009	-0.112	1.0%		-0.011	-0.140	1.0%		-0.009	-0.134	1.0%
Life remaining x Disruption (to female reproductive functioning) at level 2 x Female		-0.004	-0.058	1.0%		-0.004	-0.049	1.0%		-0.005	-0.076	1.0%
Life remaining x Disruption (to female reproductive functioning) at level 3 x Female		-0.013	-0.170	1.0%		-0.014	-0.187	1.0%		-0.010	-0.150	1.0%
Life remaining x Impaired blood sugar control at level 4 x Progression of Organ Damage present at level 3						0.005	0.064	5.0%		0.009	0.132	1.0%
Life remaining x Impaired blood sugar control at level 4 x Disruption (to female reproductive						0.003	0.035			0.001	0.022	

functioning) at level 3 x Female												
Life remaining x Triglycerides present at level 3 x Disruption (to female reproductive functioning) at level 3 x Female						-0.001	-0.017			-0.008	-0.121	5.0%
Life remaining x Progression of Organ Damage present at level 3 x Triglyceride present at level 3						0.009	0.113	1.0%				
Life remaining x Presence of Organ Damage at level 3 x Disruption (to female reproductive functioning) at level 3 x Female						0.004	0.046					
Life remaining x Progression of Organ Damage at level 3 x Triglyceride present at level 3										0.016	0.233	1.0%
Life remaining x Amputation present x Ability to perform work impaired										-0.009	-0.139	1.0%
Life remianing x Amputation present x Depression present										-0.001	-0.008	
Life remianing x Amputation present x Heart damage present										-0.011	-0.160	1.0%
Life remianing x Amputation present x Impaired blood sugar control at level 4										-0.011	-0.167	1.0%
Life remianing x Amputation present x Progression of Organ Damage present at level 3										0.014	0.208	1.0%
Life remianing x Amputation present x Retinopathy present										-0.012	-0.182	1.0%
Life remianing x Ability to perform work impaired x Depression present										-0.013	-0.187	1.0%
Life remianing x Ability to perform work impaired x Heart damage present										-0.007	-0.109	1.0%
Life remianing x Ability to perform work impaired x Impaired blood sugar control at level 4										-0.007	-0.108	5.0%
Life remianing x Ability to perform work impaired x Progression of Organ Damage present at level 3										-0.007	-0.099	1.0%
Life remianing x Ability to perform work impaired x Retinopathy present										-0.011	-0.161	1.0%
Life remianing x Depression present x Heart damage present										0.001	0.011	
Life remianing x Depression present x Impaired blood sugar control at level 4										-0.024	-0.359	1.0%
Life remianing x Depression present x Progression of Organ Damage present at level 3										-0.016	-0.238	1.0%
Life remianing x Depression present x Retinopathy present										0.010	0.145	1.0%

Life remianing x Heart damage present x Impaired blood sugar control at level 4										-0.002	-0.029	
Life remianing x Heart damage present x Progression of Organ Damage present at level 3										-0.010	-0.142	1.0%
Life remianing x Heart damage present x Retinopathy present										-0.006	-0.082	10.0%
Life remianing x Impaired blood sugar control at level 4 x retinopathy present										-0.003	-0.044	
Life remianing x Progression of Organ Damage present at level 3 x retinopathy present										-0.007	-0.098	1.0%
Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Progression of Organ Damage present at level 3										-0.002	-0.036	
Life remianing x Amputation present x Disruption (to female reproductive functioning) at level 3 x Female										0.000	-0.003	
Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Ability to perform work impaired										0.001	0.015	
Life remianing x Depression present x Disruption (to female reproductive functioning) at level 3 x Female										0.009	0.128	1.0%
Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Heart damage present										-0.006	-0.096	10.0%
Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Retinopathy present										-0.001	-0.015	
Log-Likelihood Ratio		-7673.853				-7663.531				-7555.155		
Mean Decrement		-0.089				-0.067				-0.063		
Variance across Decrements		0.058				0.051				0.034		

B15: Figure 33 (page 240) of the CS shows a comparison of the utility decrements obtained by the DCE with some values obtained from the literature.

- Some important utilities e.g. hypoglycemia, for which there is rich literature available have not been included. Please provide a comparison between DCE and literature-based utility decrements for all the utility decrements included in the model. When such a comparison is not possible please provide some discussion on the validity of the obtained utilities.
- The purpose of this validation exercise is not clear. Differences between DCE and published values appear to be large in some cases, but no consequences are discussed in the CS. Please explain what criteria are applied to assess the face

validity of the disutility values of the DCE, and what should be done if the DCE values lack face validity.

Response: Lipodystrophy is a rare disease and existing evidence regarding quality of life specific to lipodystrophy is not available in the literature. However, some attributes of lipodystrophy also occur as part of other conditions and thus estimates of utility are available. We choose to limit our comparison of utility decrements to a broad survey of the general public that included some overlapping clinical symptoms. We did not compare our estimated utility decrements to utility decrements derived for specific diseases as these disease-specific estimates likely reflect disease-specific disutility and not attribute specific disutility. The comparison is solely meant to be illustrative and we acknowledge that uncertainty exists around the disutility associated with each attribute and with lipodystrophy as a whole. To this end, a range of utility decrements are included in the DSA and the model allows for the user to override specific utility decrement inputs.

In response to this request, however, we have conducted a brief review of recent literature and compiled estimates of utility decrements for attributes similar to those we estimate. We were only able to locate estimated decrements from the literature for a subset of our attributes. Note that many important differences in the definitions of our attributes and those we find in the literature may remain. We agree with the reviewers that a more thorough review that identifies similar attributes from the literature would help identify whether our estimates are atypical. Having said that, from the table below, we can tentatively conclude that our estimates tend to be smaller (in absolute value) than those we find in the literature, and are always smaller than the upper bound of the range found in the literature.

Table 21: Comparison of estimated utility decrements with estimates from published literature

Attribute	Estimated value	Confidence interval	Range from literature
Liver abnormality(37-40)	-0.15	−0.17; −0.13	-0.201 to -0.98
Kidney abnormality (40)	-0.13	−0.14; −0.11	-0.1 to -0.475
Pancreas abnormality(41)	-0.13	−0.14; −0.11	-0.05 to -0.725
Disruption to female reproductive functioning - Infertility(42)	-0.17	−0.20; −0.14	-0.166 to -0.18
Chronic Pain (43-45)	-0.15	−0.17; −0.13	-0.34 to -0.59
Nerve damage (Neuropathy)(46-49)	-0.16	−0.18; −0.13	-0.24 to -0.6
Amputation (e.g. toes, limb)(47, 50-52)	-0.27	−0.29; −0.25	-0.22 to -0.81
Impaired blood sugar control – Achieved goal with hypoglycemia(50, 53)	-0.06	−0.08; −0.04	-0.11 to -0.30

Costs

B16: **Priority question:** The primary analysis is based on the availability of multiple vial sizes (i.e., 11.3, 5.8, and 3 mg vial sizes). However, only the 11.3 mg vial is currently available. An anticipated availability of 3 months for the smaller vial sizes is described in the submission. Please confirm the certainty of this anticipated availability.

Response: The primary analysis is based on the availability of multiple vial sizes (i.e., 11.3, 5.8, and 3.0 mg vial sizes). Only the 11.3 mg vial size will be available on approval of the Marketing Authorisation(MA). Sufficient stability data will be available at the time of MA to allow for the immediate submission of a Type IB variation for the 5.8 and 3.0mg vial sizes. Based on the available data and the similarity of manufacturing procedure to the 11.3 mg vial, we expect to achieve approval of these smaller vials within 3 months of submission of the variation.

B17: The calculation of the weighted average price of metreleptin is unclear (in sheet "Drug Costs"), especially the column "assumed Cambridge average dose following titration (TBC)". Please provide details of the dose estimations and the calculation of the weighted average price of metreleptin.

Response: A clinician at Addenbrooke provided current information regarding the metreleptin doses received by patients enrolled in the early access program, and based on these daily doses, we categorized patients as requiring a small, medium, or large vial per day. The proportion of patients receiving each size of vial was multiplied by the annual cost of treatment for each vial size to derive an average per patient annual metreleptin cost. We recognize that there is uncertainty around the distribution of patients across vial sizes and therefore include sensitivity analyses around average per patient annual cost of metreleptin

B18: Drug administration costs such as home delivery and self-administration training are not separately included in the model as these activities will be funded by the company at no additional cost to patients or NHS. Please confirm that the company will also fund these costs in the future.

Response: Aegerion can confirm that drug administration costs such as home delivery and self-administration training will be funded by Aegerion in the future.

B19: "Additional resource use costs, such as laboratory tests and office visits, are difficult to quantify given the heterogeneity of disease characteristics and lack of quality data. In this model, the resource use costs are assumed to occur equally to both metreleptin treated and standard of care patients". Please justify the plausibility of this assumption from clinical trials, literature and/or experts' opinion.

Response: This assumption was based on the relatively low cost of laboratory tests and offices visits relative to the cost of metreleptin, and was not based on literature or expert opinion.

B20: Costs of standard of care are estimated at £3,000. Please explain how these costs of standard of care are estimated, and please separate all costs into resource use in natural units and unit cost.

Response: The £3,000 in medical costs associated with SoC is applied equally to patients in both the metreleptin and SoC arms of the model. It is not an estimate, but rather a nominal figure, and is merely meant to account for ongoing routine costs of medical care for patients with lipodystrophy. This input can be set to zero in the model with minimal impact on the ICER.

B21: According to the CS, costs per patient with an abnormality are estimated with the following formula: (Number of lipodystrophy-related inpatient stays per annum per patient/ Fraction of patients with an abnormality) * Cost per inpatient stay. However, in the model, it seems like costs per patient with an abnormality are estimated differently to this formula. Please explain how costs per patient with an abnormality are estimated in the model and whether this is consistent with the formula in the CS.

Response: This formula was applied to underlying data regarding number of inpatient stays and associated costs. The resulting values were directly entered into the model as the costs associated with each type of abnormality. Organ abnormality costs were assigned to each patient in each period of model by multiplying the cost of the abnormality by the probability that the patient was still alive in the period and by the probability that the patient had the specific organ abnormality in the period

B22: In the base-case analysis, no costs are associated with hyperphagia, PCOS, inability to perform school or work, impaired physical appearance, or abnormal laboratory levels, since the costs of these attributes likely vary substantially and are hard to quantify. Please justify the plausibility of this assumption from clinical trials, literature and/or experts' opinion. Please explain why no assumptions based on literature were made to estimate these costs. Subsequently, the submission states: "As these attributes are more likely to be present in patients who do not receive metreleptin, including £0 in associated costs is conservative". Please provide any evidence for this statement (i.e. that these attributes are more likely to be present in patients who do not receive metreleptin).

Response: Lipodystrophy is a rare disease and very limited information is available about the associated economic burden. We hypothesize it is likely that the direct medical costs associated with these attributes were highly variable and may be different for LD patients than for patients with similar characteristics due to other diseases.

Data regarding these attributes were collected as part of the NIH Follow-Up study and reflect the extent to which patients experience each attribute before metreleptin treatment and after metreleptin treatment. These attributes were more prevalent prior to metreleptin treatment than after metreleptin treatment. In the model, SoC patients are assigned baseline (pre-treatment) values for each attribute in all periods of the model, and thus these attributes are more likely to be present in the SoC arm of the model than in the treated arm. The functionality of the model allows for costs to be entered for each of these attributes, and entering costs for them will increase the costs associated with the SoC arm relative to the metreleptin arm of the model. Please also note that while the costs associated with these attributes are hard to quantify and thus set to zero, the quality of life impact on patients is substantial and well documented via interviews with patients and care-givers.

B23: Please provide all details of the estimation of the costs per patient with abnormality (Table D40). Please explain why no additional costs were associated with triglyceride and glucose control and badly controlled triglyceride and glucose levels.

Response: Organ damage costs were estimated as follows:

1) For each organ, costs associated with an inpatient hospital stay were computed using the HRGs on table D39. This yielded values of £11,888 for heart (reflecting costs associated with coronary artery bypass), £16,556 associated with kidney (reflecting pre-transplant, transplant, and follow-up costs), £22,104 associated with liver, and £1,301 associated with pancreas.

2) Clinical experts were asked to provide information about the fraction of lipodystrophy patients who had an inpatient stay for each type of organ, and suggested that 6% had a heart related inpatient stay (average .06 stays per patient), 2% had a kidney related stay (.02 stays per patient), 2% had a liver related stay (.02 stays per patient), and 1% had a pancreas related stay (.01 stays per patient).

3) The proportion of lipodystrophy patients with each type of abnormality at baseline in the NIH Follow-Up study was then combined with these values to compute the cost associated with each abnormality.

B24: The model base case does not include costs to caregivers (formal care through the NHS), costs associated with routine monitoring, and drug administration costs such as home delivery and self-administration training (see 12.3.9). Please justify the plausibility of this assumption from clinical trial, literature and experts' opinion.

Response: These costs are not included in the model base case because Aegerion plans to provide support for drug administration cost such as home delivery and self-administration training as part of the cost of metreleptin; thus no additional costs would accrue. This assumption in the model is based on Aegerion's plan, and not literature, expert opinion, or the clinical trial.

B25: In the model, it seems that a proportion/weight is applied to the cumulative number of organ abnormalities to calculate the probability of a specific organ abnormality. However, it is not clear how these proportions/weights (e.g. Kidney, Liver, Heart, and Pancreas) among all organ abnormalities were derived. Also, the application of these weights seems to differ between cost and utility calculations in the model (in "COS_Organ" and "TDU_Organ" sheets). Please explain how these weights are derived, how they are apply to the cumulative number of organ abnormalities in cost and utility calculations and explain the differences in the cost and utility calculations.

Response: Ratio weights are derived from the assignment weights in cells J54-J57 in the "Organ Abnormality Progression" tab. Assignment weights equal the baseline prevalence of each organ abnormality among all patients in the NIH Follow-Up study. Each ratio weight is the relevant assignment weight divided by the sum of assignment weights. The model uses these weights in the organ abnormality-based cost and utility calculations in periods for which real-world data on a patient's organ abnormalities are not fully available. In the absence of real-world data, the model estimates a level of organ abnormality but does not specify which organs are abnormal. Therefore, in order to estimate decrements and costs associated with the organ abnormality level, the model applies ratio weights so that decrements and costs of more prevalent organ abnormalities are given greater weight in the calculation.

B26: **Priority Question:** Resource use is identified by two clinical advisors who treat lipodystrophy at Addenbrooke's Hospital. Please provide more details of the communication between the company and the clinical experts for all KOL based assumptions. Please include the anonymised information about the clinical experts, , the list of expert recommendations and justifications for clinical assumptions used in the model (e.g. the assumed Cambridge average dose of metreleptin), questionnaires completed by the clinical advisors, etc and if possible please also provide minutes of any meetings.

Response:
The average dose for metreleptin in the model is based on the following dose mix:

Table 22: Current dose mix at Addenbrooke's

Vial Size mg (A)	Assumed Cambridge dose following titration (B)	Proportion of Dose (C)
10mg	3.00	11.54%
5mg	18.00	69.23%
2.5mg	5.00	19.23%

Where column C is equal to column B divided by the sum of column B.
The information in column B is based on i) the current dose mix at Addenbrookes among lipodystrophy patients treated there with metreleptin, and ii) adjusted for potential future increase in dose if such an increase was seen as likely in the future (e.g. due to age, etc.).

Specifically, for (i), the following information was provided by Addenbrookes' clinicians:

Table 23: Adjusted dose for potential increase in dose

Vial Size mg (A)	Current Cambridge dose (D)	Proportion of Dose (E)
10mg	3.00	11.54%
5mg	12.00	46.15%
2.5mg	11.00	42.31%

For ii), clinicians at Addenbrookes were asked to assess for each dose the number of patients who may be switched to a higher dose in the future. They considered that 6 patients on 2.5mg would be switched on 5mg over time.
The Clinical experts consulted were two out of the three clinicians that manage lipodystrophy patients at Addenbrookes. We believe a representative of this team will be attending the NICE committee meeting and should be able to confirm these assumptions if necessary. The information was collected over a combination of e mail interactions, phone calls and an in-person meeting. No minutes of these calls/meeting were taken (beyond the assumptions above).
The average dose assumption used is conservative from a UK perspective as it assumes that all patients are in their long-term UK dose for all time periods.

The insights from clinicians at Addenbrookes were also sought to capture the impact of lipodystrophy/metreleptin on other resource utilization (e.g. medical costs). The numbers on medical costs associated with organ abnormalities and their treatment are based on these exchanges. Still the clinicians at Addenbrookes found it extremely challenging/impossible to

come up with a single point estimate, noting the large variability of experiences across patients. It should be noted however that the DSA conducted suggested a limited impact of these parameters on the cost effectiveness assessment.

Adverse events

B27: Explain why no adverse events other than hypoglycaemia were incorporated in the model (e.g. neutralizing antibodies, fatigue, injection site issues, decreased weight, impact of pancreatitis following discontinuation etc.). Please include all clinically relevant adverse events in the economic model. Discuss any implications of excluding adverse events in the economic analyses.

Response: When reviewing whether to include particular AEs in our cost effectiveness analysis, beyond their prevalence, considerations included: i) whether these AEs were likely caused by metreleptin (vs. were a feature of lipodystrophy, since no control arm was available), ii) the availability of control data (e.g. baseline or pre-baseline information) and iii) whether the potential impact on cost-effectiveness could be significant (e.g. vs. marginal).

Fatigue accounted for 7.3%-9.1% of total treatment-emergent AEs within lipodystrophy subgroups in the NIH 991265/20010769 study. In discussions with Dr. Brown at NIH, her opinion was that there was no significant increase in fatigue associated with the use of metreleptin. Furthermore, adequate information on fatigue prior to treatment with metreleptin was not available from chart data at NIH, thus a decision was made not to include consideration of fatigue in our cost-effectiveness assessment. Subsequently, we have found in our patient research interviews, including based on the subset of UK patients interviewed, that the real-world prevalence of fatigue in lipodystrophy patients may be underestimated (vs. the clinical study estimates above), that extreme fatigue can be a major feature of the disease for some patients, and that some patients appear to have experienced an improvement in their fatigue symptoms following the use of metreleptin.

Based on the present neutralizing antibody assay, AEs of neutralizing antibodies accounted for up to 6.1% of all AEs reported in GL patients, and 0% of all AEs reported in PL patients, and for the majority of these patients the impact on efficacy was transient. Since markers of efficacy are already factored in the cost effectiveness analyses, and given the limited treatment alternatives to metreleptin, further inclusion of neutralizing antibody considerations, though potentially important clinically, was not seen as likely to have a large impact on the cost-effectiveness assessment.

All injection site issues in the NIH 991265/20010769 study were moderate, non-serious, and did not lead to treatment withdrawal. The prevalence of such issues was low, occurring in between 6-7% of patients, depending on the lipodystrophy subgroup (GL vs PL) analysed15. Consequently, their impact on cost-effectiveness considerations was seen as likely to be marginal and they were not included in the analyses.

[15] Source: M2.7.4

AEs of weight decreased occurred commonly in the NIH 991265/20010769 study: accounting for 25.8% of total AEs reported in GL patients, and 4.9% of total AEs reported in PL patients. However, excessive weight loss concerns were generally addressed by dose modification/reduction. The potential reduction in the cost of metreleptin (to the extent that some patients with excessive weight loss are moved to lower doses) was not factored in the cost-effectiveness analyses. As such the current cost-effectiveness analysis may be conservative in this respect.

For pancreatitis events if patient discontinues metreleptin therapy, please see answer to question A13.

Note: All AE frequencies reported above are sourced from Study NIH 991265/20010769 CSR, Table 14.3.1.27A

Budget impact analysis

B28: The eligibility for lipodystrophy (13.1) and the uptake rate of metreleptin (13.2) are based on expert clinical opinion. Please provide all details of the data used for these assumptions and provide the budget impact calculations within the model.

Response: The eligibility used in the analysis was [redacted] patients in year 1 rising to 44 patients in year 5. This was based on December 2017 Early Access Programme (EAP) data which refers to the number of patients ([redacted]) receiving metreleptin ([redacted]) at the most recent EAP datacut. For the number of new patients expected to be eligible each year clinical opinion of two new GL patients and four new PL patients (n=6 in total) each year was based on estimations from the two clinical experts at Addenbrookes. These two clinical experts are the clinicians managing the majority of the patients on the EAP. Hence, the assumption was estimated based on the experience of these experts in treating lipodystrophy, with consideration of the EAP data patient numbers.

The uptake rate used was estimated as 85% in year 1 rising to 90% in year 5 based on company forecast assumptions. It is expected that uptake for metreleptin would be reasonably high for those patients eligible given the nature of the condition and alternative treatment options consisting of SoC only. Aegerion expect uptake to be high but due to potential barriers to treatment all patients may be unwilling or unable to receive metreleptin e.g. undesirable daily metreleptin injections, long travelling distance for patients to the single centre of care at Addenbrookes from their residence, satisfaction with the current SoC received.

The discontinuation rate, noted as the mortality in section 13.1 of the submission, is an included company assumption to reflect a more realistic clinical practice where a small number of patients each year may discontinue the drug due to patient preference, clinical recommendation, or death, and hence stop treatment with metreleptin and SoC.

The budget impact calculations for all scenarios (BC1, BC2, BC3, BC4) have been provided in a separate excel document. These scenarios are:

- BC1: metreleptin 10mg dose and SoC, compared with treating only with SoC at list price

- BC2: metreleptin available in three different vial sizes (11.3mg, 5.8mg, 3mg) and SoC, compared with treating only with SoC at list price
- BC3: metreleptin 10mg dose and SoC, compared with treating only with SoC at PAS price
- BC4: metreleptin available in three different vial sizes (11.3mg, 5.8mg, 3mg) and SoC, compared with treating only with SoC at PAS price.

Please note scenario BC4.1 has an equivalent budget impact to BC4.

Validation

B29: Priority Question: Please provide all the details of the validation exercise mentioned in Section 12.7 of the CS. Did the validation exercise include all the steps (internal validation, cross-validation, etc…) as explained for example in the AdvisHE (https://advishe.wordpress.com/) tool? If not, please include these steps as well.

Response: The validation exercise mentioned in section 12.7 specifically involved discussing the conceptual model, assumptions, and inputs with the clinical experts. Additional validation efforts were also completed, although not all types of validation were feasible due to the rare natural on lipodystrophy and lack of prior cost-effectiveness analyses. We will document these additional efforts and limitations using the AdvisHE template and provide by Friday March 2

Sensitivity/scenario/subgroup analyses

B30: Priority Question: The ERG has identified a number of issues/discrepancies related to the sensitivity/scenario analyses

- **(B30a)** Please provide the criteria for the parameters to be included into PSA and DSA. Parameters such as the time horizon, and discount factor should not be included in the sensitivity analyses, as their uncertainty can be characterised under methodological uncertainty and therefore should be explored in scenario analysis. Metreleptin price/costs should not be explored in sensitivity analyses, as well. If there are factors that impact annual metreleptin acquisition costs (such as patient weight), they should be varied independently from metreleptin price.

Response: We would like to clarify that per patient cost for metreleptin was included in the sensitivity analyses due to uncertainty about average per patient dose. The bounds used in this sensitivity have been updated to more clearly reflect the source of uncertainty.

- **(B30b)** It is not clear how the upper and lower limits for the parameters included in the DSA were obtained, as these are not the upper and lower 95% CI limits. Please explain where these originate from.

Response: As many model parameters were assumption-based, ranges were selected to illustrate a wide set of reasonable values. Parameters that were derived from analysis of the NIH Follow-Up or Natural History data now include 95% CI limits in the DSA.

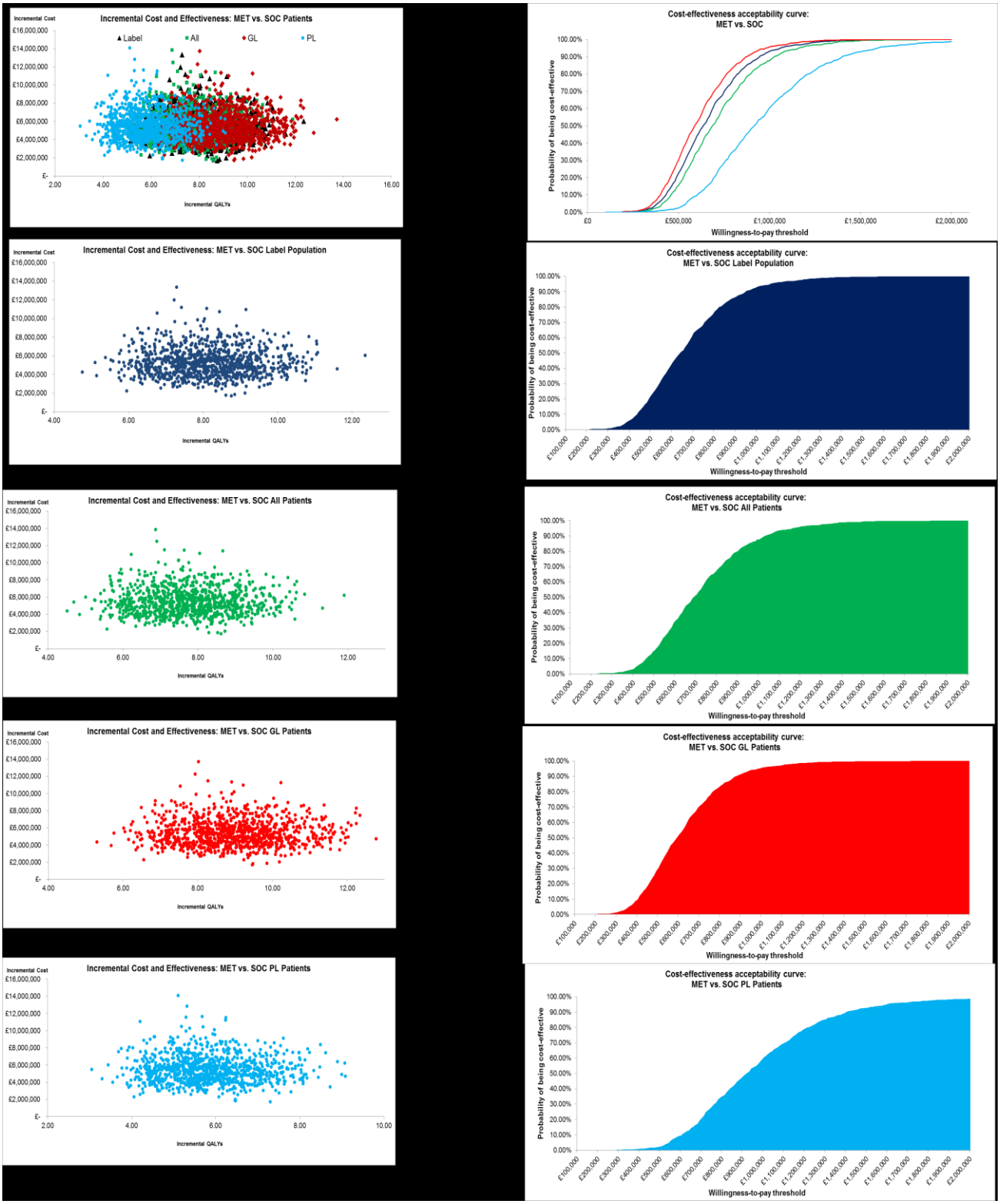
- **(B30c)** It seems that the standard deviation was used for each parameter (instead of standard error), and some of the standard deviation estimates are implausible in Table D43 (i.e. negative). Furthermore, their source references are unclear. Also, for some of the parameters, the probability distribution chosen seem to be incorrect (e.g. normal distribution for disease progression or discontinuation rates, which might lead to negative estimates). Please explain where the uncertainty estimates are generated from for each parameter, and the rationale behind the choice of the distributions.

Response: As many model parameters were assumption-based, a value of 25% of the parameter base value has been used as the standard deviation of the parameter for the purposes of the PSA. Specifically, these values are assumptions, and are used to specify the width of the distribution from which alternative values of the parameter are drawn. When the base parameter value is negative, this distribution width is set to 25% of the absolute value of the parameter. Distributions have also been updated to better reflect the likely properties of each parameter -- for example, a Beta distribution is now used for the transition probabilities. The associated labeling and display issues in the model have also been corrected.

- **(B30d)** Please provide more details about how the PSA is conducted: inner and outer loop sizes, how patients are selected (with/without replacement), whether the patients are the same in the two arms, etc. Please confirm whether DSU guidelines (TSD 15) for conducting PSA in a patient-level model were followed or not. Also please provide the average and 95% CI of the PSA results for total/incremental costs, total/incremental QALYs for the base case and all subgroup analyses.

Response: The PSA is a simulation of alternative parameter values, and does not vary the set of patients included in the model. Please see results of updated PSA below. The results from the PSA with the PAS pricing assumptions can be provided upon request.

Figure 9: PSA output for multiple vial price



- **(B30.e)** Please explain the rational of the multi-way scenario analysis assumptions, why it was presented as base case 4.1 in the executive summary, and the details of the changes (e.g. further justification for the resolution of heart abnormalities)

Response: The multi-way scenario illustrates a set of plausible alternative assumptions that were not included in the base case in an attempt to be conservative. Specifically, these alternate assumptions reflect places in which we believe estimated values may help understand the true benefit of metreleptin either due to limited data (e.g., heart abnormality improvement was not directly observed, but was noted anecdotally) or due to the unusual nature of some lipodystrophy symptoms (e.g., members of the general public may not have understood how hyperphagia differs from usual "hunger").

- **(B30.f)** Please provide guidance explaining how to implement each of the scenarios in Table D51 in the model (which cells need to be changed, which controls should be activated, etc.)
- Please provide new PSA and DSA results with an appropriate list of parameters, having appropriate upper and lower limits, appropriate PSA methodology, mean and standard error values and probability distributions.
- It seems like in the subgroup analyses, for each subgroup, the average results of the patients that fall into the corresponding subgroup are calculated. This approach assumes that there is no difference in terms of transition probabilities (for disease progression or survival), health care resource utilisation and utilities among all subgroups. Please justify if this assumption is plausible from the patient level data from the NIH Follow-Up and Natural History studies, otherwise incorporate the subgroup specific inputs in the model.

Response: In order to implement the 10mg dose scenario, input the price of 10mg Metreleptin vial (Cell F62) in the “User Vial Price Input” cell (Cell H38) in the “Drug Costs” tab

In order to implement the multiple vial size scenario, please set the “Discount Applied” (Cell G38) to 0%.

Due to the rare nature of lipodystrophy and the small size of both the NIH Follow-Up study (n=112) and the Natural History study (N=178), it was not feasible to estimate transition probabilities and hazard ratios for each patient subgroup. As survival did appear to be significantly different for GL and PL patients, separate survival curves were used and the mortality hazard ratio associated with organ abnormalities was computed separately for GL and PL. Organ abnormality progression in the Natural History study appeared to be less associated with lipodystrophy sub-type, especially once an initial organ abnormality was observed, and thus we felt it was plausible to use a single set of transition probabilities for both groups. The model is set up to accept different probabilities for GL and PL and thus if additional data are available in the future, this assumption could be updated.

Impact beyond direct health benefits

B31: In the CS, in section 14.1, it is mentioned that after metreleptin initiation, the percentage of not working or part-time working caregivers was decreased around 80% (From 35% at the baseline to 7% after follow-up). Please clarify when the latter figure (7%) was measured. Please clarify if this decrease is attributable to the treatment or the fact that the patients grow up.

Response: The latter figure reflects caregivers' work status as of the most recent NIH visit. This reduction holds both for patients who are still under 18 at last visit and those who are over 18.

B32: In the CS, in section 14.3, type 2 diabetes (T2DM) indirect costs for UK were provided as a proxy. Please justify why indirect costs for T2DM would be a proxy for the indirect costs for LD. . Also, please provide more details and the source of the hospitalisation figures (20% of LD are hospitalized at least once a year, with some hospitalised more than 5 times a year).

Response: We have not identified any studies reporting on the indirect costs associated with LD. However, diabetes is one of the most common complications of LD - for example, in study NIH 991265/20010769 70% of GL patients and 84% of PL subgroup patients had diabetes at baseline. Therefore, in the absence of studies in LD, studies reporting on T2DM in the UK were used as an example of the indirect costs that may be associated with just one of the complications of LD.

B33: Please provide estimates for the indirect health care costs due to additional years after receiving metreleptin.

Response: The model has not been designed to include indirect health care costs (i.e. costs not related directly to LD sequelae) associated with additional life years estimated for metreleptin over SoC. All direct healthcare costs associated with organ damage progression and related costs have been included in the analysis and are not major drivers influencing the cost-effectiveness of metreleptin, and it is not expected that any indirect health care costs would be of any magnitude to influence the cost-effectiveness results. There may be additional end of life costs but these will affect both treatment groups and so not be expected to impact on the cost-effectiveness results.

Section C: Textual clarifications and additional points

C1. Section 12.2.4 of the CS includes the following text:
'Hypoglycaemia was included in the cost-effectiveness analysis as an adverse event. Only treated patients were eligible to experience hypoglycemia and during the NIH study data period, a count of observed hyperglycemia events was assigned to each patient. After the end of observation, an annualized count of hyperglycemia events was assigned to remaining model periods.'
Please confirm that the above text should refer to hypoglycaemia and not hyperglycemia throughout.

Response: The text should refer to hypoglycaemia and not hyperglycemia throughout.

C2. Table C20 'Critical appraisal of study NIH 991265/20010769' is incomplete. Please provide the missing content for the following two items:
'Was the follow-up of patients complete?'
'How precise (for example, in terms of confidence interval and p values) are the results?'

Response: Please see the full table, including the missing items.

Table 24: Table C20: Critical appraisal of study NIH 991265/20010769

Study name: NIH 991265/20010769		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	The patient population was representative of a defined population. The patients had low leptin levels (<12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years) and at least 1 metabolic abnormality out of diabetes mellitus; fasting insulin concentration >30 µU/mL, and/or fasting triglyceride concentration >2.26 mmol/L or postprandially elevated triglycerides >5.65 mmol/L when fasting was clinically not indicated (e.g., in infants); these are the hallmarks of this syndrome, i.e., insulin resistance with diabetes mellitus and hypertriglyceridaemia. Patients were recruited from different regions across the world.
Was the exposure accurately measured to minimise bias?	Yes	Exposure was clearly defined and accurately measured. The measurement of exposure was objective i.e dose and duration, including average (mean [SD], median and range) for daily dose (mg/day), and weighted average dose (mg/kg).
Was the outcome accurately measured to minimise bias?	Yes	The study's efficacy endpoints were objective measurements, including the co-primary endpoints of HbA1c and triglycerides. These measurements were primarily obtained at a single laboratory and thus treatment effects could be appropriately evaluated. The efficacy endpoints were clinically relevant to the patient and the progression of disease.
Have the authors identified all important confounding factors?	Yes	Potential confounding factors included: concomitant medication use, sex, race, age, weight, height, body weight category, BMI, region, LD subtype (CGL, AGL, FPL, APL), gene mutation (LMNA, PPARg, Seipin, AGPAT-2, ZMPSTE24, Other, and not applicable), baseline laboratory values.

Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	In addition to the FAS, efficacy was analysed on the CFAS, which included all patients in the FAS who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid lowering therapies), prior to Month 12. Data for all anti-diabetic or lipid lowering therapies, including type, dose, regimen, and route of administration, underwent medical review and patients who had these types of medications added or doses increased that may have had an impact on the efficacy endpoints were excluded from the CFAS. Patients were excluded separately based on the type of medication that was added or increased, e.g., patients with potentially confounding anti-diabetes medications were excluded from the analyses of HbA1c and those with potentially confounding lipid-lowering therapies were excluded from analyses of triglycerides. In general, the results for the efficacy analyses were consistent for the FAS and the CFAS. In addition, subgroup analysis were conducted based on a number of baseline characteristics to show whether treatment effects were observed consistently across relevant populations. including: LD subtype (AGL, CGL, FPL, and APL); age (age categories <6, ≥6 to <12, ≥12 to <18, < 18, and ≥18 years old); region (US, EU, EU and Eastern Mediterranean, and Other); presence of metabolic abnormalities at baseline (HbA1c [<6.5 and ≥6.5%], ≥7%, ≥8% and fasting triglycerides [<2.26 mmol/L and ≥2.26 mmol/L / <200 and ≥200 mg/dL, ≥5.65 mmol/L / ≥500 mg/dL; and between ≥2.26 and ≤5.65 mmol/L / ≥200 and ≤500 mg/dL]); concomitant insulin, anti-diabetic medications and lipid-lowering medications at baseline; baseline leptin levels (<12 ng/mL / ≥12 ng/mL, primary efficacy analysis only) (see Section 9.6.1.5)
Was the follow-up of patients complete?	Yes	Only one patient was lost to follow-up (see Section 9.4.7)

How precise (for example, in terms of confidence interval and p values) are the results?	Yes, the precision of the results is reasonable	The following results with 95% CIs were reported were reported: GL patients: mean change from baseline to Month 12/LOCF for HbA1c was -2.2% (95% CI: -2.7, -1.6) and the mean percent change in triglycerides was -32.1% (-51.0, -13.2) PL subgroup[a] patients (excluding outlier patient): mean change from baseline to Month 12/LOCF for HbA1c was -0.9% (95% CI: -1.4, -0.4) and the mean percent change in triglycerides was -37.4% (-57.2, -8.6). The majority of patients in both the GL group and the PL subgroup achieved meaningful reductions in both HbA1c and triglycerides.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		
Abbreviations: AGL = aquired generalised lipodystrophy; APL = aquired partial lipodystrophy; BMI = body mass index; CFAS = Controlled Concomitant Medication Full Analysis Set; CGL = congenital generalised lipodystrophy; CI = confidence interval; EU = European Union; FAS = full analysis set; FPL = familial partial lipodystrophy; GL = generalised lipodystrophy; HbA1c = glycated haemoglobin; LD = lipodystrophy; LOCF = last observation carried forward; PL = partial lipodystrophy; SD = standard deviation; US = United States		

Source: Study NIH 991265/20010769 CSR(33)

C3. Table C15 (CS, page 78) is headed 'Summary methodology for study FHA101', but appears to contain both a repeat of information for study NIH 991265/20010769 and information for study FH101. Please provide a corrected version of this table.

Response: Please see the corrected version of this table.

Table 25: Table C15: Summary of methodology for study FHA101

Study name	FHA101
Objective	To provide expanded access to metreleptin to patients with LD and associated metabolic disorders such as diabetes mellitus and/or hypertriglyceridaemia and to test the safety and efficacy of metreleptin in this population of patients.
Location	Six centres in the US*
Design	Open-label, expanded-access
Duration of study	Continuous enrolment over 6 years (2008-2014)*: Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months
Patient population	Patients with GL or PL (including subgroup of PL patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L)
Sample size	N=41 (GL= 9; PL=32; PL subgroup=7)*
Inclusion criteria	Male or female ≥5 years old Physician-confirmed LD as defined by evidence of generalised (whole body) or partial (limbs) loss of body fat outside the range of normal variation

	Diagnosed with at least 1 of the following 2 metabolic disorders: • Diabetes mellitus • Hypertriglyceridaemia as defined by fasting triglyceride concentrations >2.26 mmol/L (>200 mg/dL)
Exclusion criteria	Diagnosed with human immunodeficiency virus (HIV) infection Clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the Investigator Acquired LD and clinically significant haematologic abnormalities (such as neutropaenia and/or lymphadenopathy) Known infectious liver disease Known allergies to E. coli-derived proteins or hypersensitivity to any component of study treatment
Statistical tests*	The primary and key secondary efficacy analyses were performed primarily on the FAS (all patients who received at least 1 dose of study drug and had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit). The primary and key secondary endpoints were summarised using descriptive statistics and 95% CIs. P values for the primary endpoints were computed using paired t-tests to determine if the change from baseline to Month 12 was significantly different from 0, at a one-sided α-level of 0.025. The LOCF method was used to impute any missing Month 12 results. The imputation only took into account results that were at least 6 months (180 days) post-baseline. Thus, analysis of primary efficacy endpoints included all patients that have baseline and at least Month 6 measurements. A MMRM analysis was used to assess changes over time for the entire duration of the study.
Primary outcomes	• Actual change from baseline in HbA1c at Month 12 • Percent change from baseline in fasting serum triglycerides at Month 12
Key secondary outcomes	Proportion of patients achieving target actual decreases of: • ≥1% actual decrease in HbA1c or ≥30% decrease in fasting triglycerides at Month 12 • ≥1.5% decrease in HbA1c or ≥35% decrease in fasting triglycerides at Month 12 • ≥2% actual decrease in HbA1c or ≥40% decrease in fasting triglycerides at Month 12 • Actual and percent change from baseline for fasting glucose levels at Month 12
Other relevant secondary outcomes	• Actual change from baseline in HbA1c at each post-baseline visit • Percent and actual change from baseline in fasting serum triglycerides at each postbaseline visit • Actual change from baseline in ALT and AST at each post-baseline visit through Month 12

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; FAS = full analysis set; GL = generalised lipodystrophy; HbA1c = glycated haemoglobin; HIV = human immunodeficiency virus; LD = lipodystrophy; LOCF = last observation carried forward; MMRM = Mixed-effect Model Repeated Measures; PL = partial lipodystrophy; US = United States

Source: Clinicaltrials.gov NCT00677313(54); Ajluni 2016(17); *Study FHA101 CSR(55)

C4. There appears to be a transcription error regarding the BC2 definition – between main submission (page 15) and PAS submission. Please correct the text appropriately.

Response: We apologise for any confusion surrounding the definitions of the base case scenarios presented and any discrepancies between the main submission and PAS evidence submission.

The base case scenarios discussed in both documents should refer to:

- BC1: metreleptin 10mg dose and SoC, compared with treating only with SoC at list price
- BC2: metreleptin available in three different vial sizes (11.3mg, 5.8mg, 3mg) and SoC, compared with treating only with SoC at list price
- BC3: metreleptin 10mg dose and SoC, compared with treating only with SoC at PAS price
- BC4: metreleptin available in three different vial sizes (11.3mg, 5.8mg, 3mg) and SoC, compared with treating only with SoC at PAS price.
- BC4.1: metreleptin available in three different vial sizes (11.3mg, 5.8mg, 3mg) and SoC, compared with treating only with SoC at PAS price, with adjusted utility values (larger decrement for hyperphagia, allowance for improvement in heart abnormality)

It is expected that three different vial sizes will be approved of sizes 11.3mg, 5.8mg and 3mg which will allow dose administrations of up to 10mg, 5mg and 2.5mg respectively. Scenarios BC2, BC4 and BC4.1 consider the expected clinical practice if all these vial sizes were available, while BC1 and BC3 consider the availability of the 11.3mg vial size only. Scenario BC1 and BC2 reflect the list price of metreleptin while BC3, BC4 and BC4.1 reflect the PAS price requested.

Hence, the PAS submission correctly references BC2 but on page 14 of the main submission the sentence within the final paragraph incorrectly refers to BC2 but actually should state BC3. Therefore, the sentence corrected in the main submission should read : “Hence, an initial base case using the 10mg dose, at list price is presented (BC1), and the alternative base case for this vial size with proposed PAS price applied (BC3) is also presented (see separate PAS based economic analysis submission)”.

If there remains any confusion or discrepancies between the submission and PAS submission then we will be happy to try and resolve this further following contact from the ERG.

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Metreleptin for treating lipodystrophy ID861 - Additional responses to clarification questions 13th February 2018

Submitted by Aegerion Pharmaceuticals Ltd.

Highly Specialised Technology Evaluation (HST)
National Institute of Health and Care Excellence

Submitted 2nd March 2018

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List of Abbreviations

AGL	Acquired generalised lipodystrophy
ALT	Alanine aminotransferase
APL	Acquired partial lipodystrophy
AST	Aspartate aminotransferase
BSCL	Berardinelli-Seip congenital lipodystrophy
CE	Cost-effectiveness
CFAS	Controlled Concomitant Medication Full Analysis Set
CI	Confidence interval
CGL	Congenital generalised lipodystrophy
CSR	Clinical study report
CUH	Cambridge University Hospitals
DCE	Discrete choice experiment
DSA	Deterministic sensitivity analysis
EAP	Early Access Programme
EMR	Electronic medical records
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPL	Familial partial lipodystrophy
FPLD	Familial partial lipodystrophy, Dunnigan variety/ familial partial lipodystrophy type
GL	Generalised lipodystrophy
GPRD	General Practice Research Database
HbA1c	Glycated haemoglobin
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HST	Highly specialised technology evaluation
HSUV	Health state utility values
HTA	Health technology assessment
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICER	Incremental cost-effectiveness ratio
ISM	Individual sampling modelling
IV	Intravenous
KM	Kaplan-Meier
LD	Lipodystrophy

LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
MA	Marketing authorisation
MAE	Mean absolute error
MET	Metreleptin
MH	Moderate hypoleptinaemia
MID	Minimum important difference
MMRM	Mixed-effect Model Repeated Measures
MRI	Magnetic resonance imaging
MSM	Multi-state model
NIH	National Institutes of Health
NHS	National Health Service
NASH	Non-alcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
PCOS	Polycystic ovary syndrome
PL	Partial lipodystrophy
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RMSE	Root mean square error
RWD	Real-world data
SD	Standard deviation
SH	Severe hypoleptinaemia
SLR	Systematic literature review
SMD	Standardised mean differences
SOC	Standard of care
T2DM	Type 2 diabetes mellitus
TG	triglycerides
TTO	Time trade-off
UK	United Kingdom
US	United States
UTSW	University of Texas Southwestern

1. Overview

This document contains Aegerion's additional responses to clarification questions from the Evidence Review Group, Kleijnen Reviews Ltd.(ERG), and the technical team at NICE that were sent to Aegerion on Tuesday 13th February 2018. We provided a set of responses that addressed many questions as fully as possible on 27th February 2018. Additionally, as agreed with NICE and the ERG on the teleconference 21st February 2018, model adaptations and some supplemental analyses supporting questions B4, B7, B8, B14, and B29 were given an extended response submission date of 2nd March 2018 and are included in this submission.

In the process of preparing our responses, we recognized some inconsistencies in the organ abnormality data. We have now addressed these inconsistencies and have updated our analyses of organ abnormality progression and survival in revised responses to questions B3, B5, and B10. We have also updated the CE model outputs reported in sections 12.5-12.8 of our original submission [Metreleptin ID861 Updated CE Results.docx] and in the PAS [Metreleptin ID861 Updated PAS CE Results.docx].

2. Response to clarification questions

Please find below responses by Aegerion to each of the questions raised by the ERG, Kleijnen Reviews Ltd, and the technical team at NICE.

B4a. Please provide scenarios, in which the attributes like hyperphagia, ability to work, reproduction, physical appearance and fast disease progression do not stay at their baseline values but may change over time.

Response: We have incorporated this functionality into the model as follows:

For each attribute, patients who do not have the attribute at baseline are assumed to develop the attribute in each period with a specified probability in each year. While we do not have data regarding development of these attributes for an untreated population, we have computed a very rough annual rates for developing each attribute by dividing the total number of patients with each attribute in period 0 by the number of total patient years lived prior to metreleptin initiation (sum of age at baseline across all patients). We use this rough annual rate as the probability that a patient in the standard of care arm who does not already have the attribute develops the attribute in each period. For patients in the metreleptin arm, this annual rate is reduced by the proportion of the population who improve on the specific attribute following metreleptin initiation. The annual probabilities are user modifiable for both MET and SOC arms. With our default rates, enabling changes in these attributes over time results in an ICER of £580,216/9.63 QALYs, with 1.32 QALYs gained.

B7. **Priority Question:** Please justify why only a "last observed carried forward" approach was followed in the extrapolation of glucose and triglyceride levels. Please explore other methods for blood glucose (e.g. regression imputation or assuming a linear increase in HbA1c as in other type-2 diabetes models (http://www.core-diabetes.com/)) and triglyceride

(e.g. mean imputation) extrapolation. Also, please present a comparison of these attribute values used in the economic model with the values presented in the clinical effectiveness section.

Response (Added Mar 2): We have added basic functionality to systematically vary HbA1c and TG values over time in the March 2nd version. MET patients are each assumed to experience the same annual change in TG and HbA1c that they do during the period of observed data. SOC patients are assumed to experience an increase 0.01 percentage points of HbA1c each period and 1 mg/dL. These input values are solely assumptions, and the functionality is incorporated to allow additional explorations with the model. As discussed below, data from the Natural History study do not seem to support a specific trend and even if a trend were identified, we would be hesitant to extrapolate for the 90 years of the model.

(Feb 27): While the NIH Follow-Up study suggests improvements in HbA1c and triglyceride (TG) occur due to metreleptin treatment, there is variation in how much each patient responds and there is variation in laboratory readings over time. Rather than assuming a specific trend for each patient, we chose the LOCF approach to be conservative. Data from our Natural History study also suggests that HbA1c values for untreated patients vary over time, but do not suggest a specific trend. We chose not to use type 2 diabetes models to simulate blood glucose levels in lipodystrophy patients, as lipodystrophy is a distinct clinical condition with a distinct mechanism for elevation of blood glucose. As the costs and utility decrements associated with HbA1c and TG are already included in model sensitivity analyses, the model does reflect some of the potential uncertainty around these values. We will add some functionality to systematically vary HbA1c and TG values over time in the version of the model delivered on March 2.

In addition, the real-world data collected on longer term outcomes including organ abnormalities and mortality allow the CE model to utilize direct burden measures rather than metabolic markers alone.

Please note that the NIH Follow-Up study (used for the CE model) included the same patients as in the clinical trial (discussed in the clinical effectiveness section). The NIH Follow-Up study includes all of the HbA1c and TG reading collected as part of the clinical trial. However, the data were averaged for each patient to reflect the CE model period length of one year Specifically, period 1 values in the CE model reflect readings from 6 months after metreleptin initiation to 18 months after, period 2 values reflect the average of all readings from 18 months to 30 months, and so on.

Survival analysis

B8. Priority Question: In the company's model, the 'percentage of people alive' at the end of the time horizon is considerably higher than zero (e.g. average probability of being alive at the end of the time horizon is 26.7% in the metreleptin arm). Please provide a scenario with a long time horizon, where the average percentage of people being alive at the end is almost zero. Note that it might require some reprogramming of the model, so that it accommodates longer time horizons than 60 years (maximum).

Response: The model has now been extended to 90 years and the capping method explained in B9 has been applied. Based on the exponential survival extrapolation and the UK national life tables, the lower conditional survival probability obtained from these two survival curves is applied to calculate survival for Metreleptin and SoC patients in the model for each period; this results in more patients whose survival probabilities are derived according to their age from the UK national life table in the later model periods. By period 90, < 1% of patients are expected to remain alive in this extended model. The extended model has been used to repopulate all results in sections 12.5-12.8 of our original submission [Metreleptin ID861 Updated CE Results.docx] and all CE model outputs reported in the PAS [Metreleptin ID861 Updated PAS CE Results.docx].

Table 1: Results from extended model

Model Horizon	Life Years		QALYs		ICER	% alive at end of model
	MET	SOC	MET	SOC		
60	18.09	14.56	8.47	.27	£676,534	27%
70	18.30	14.67	8.54	.25	£673,169	14.5%
80	18.36	14.71	8.55	.25	£672,063	4%
90	18.36	14.71	8.55	.25	£671,927	.5%

B14: Priority Question: The ERG notes that additive approach followed in the submission of applying attribute disutilities in QALY derivation often leads to negative values for total QALYs (see for example the number of QALYs for SoC in Table D49). This would imply that on average, patients receiving SoC would rather be dead than living with lipodystrophy. Also, one of the two references in the CS, Ara and Brazier 2012 suggests using the multiplicative approach together with a range of sensitivity analyses. Note that the other reference, Viney et al. 2014, also shows preference for a model with interaction (possibly multiplicative) rather than additive because "interaction terms reflect their preference complementarity, namely, that two or more health problems' combined impact is less than the sum of the individual main effects". This seems reasonable in this setting when multiple attributes define the health status of a patient.

- Please adapt the analysis in 17.5.2.5 to provide disutility estimates that are fit for use in the multiplicative approach.
- Please modify the model such that it accommodates the application of the disutilities in a multiplicative way as an option and present an analysis using the estimates requested in the previous bullet point .

Response: (Please note, we have expanded our response beyond our submission of 2/27 to include multiplicative decrements and corresponding model outputs)

Regarding the "negative values for total QALYs" in Table D49, we would like to clarify that Table D49 shows the discounted expected QALYs for treated patients and those under the SoC. The negative QALY value for SoC patients is not uncommon for a condition that affects multiple attributes. Note that the EQ-5D-derived preference-based index in the Ara and

Brazier (2012) study cited in the question has a range of -0.59 to 1. The negative value of -0.6 in Table D49 pertains to the expected discounted QALYs over the model's 60 years of simulated patient trajectories and must not be interpreted as an annual QALY value.

Regarding the comment that "Ara and Brazier 2012 suggests using a multiplicative approach together with a range of sensitivity analyses", and likewise similar guidance in TSD 12: we have reviewed the referenced work and concluded that the methods discussed are not directly relevant to our analysis of DCE data. In the section below, we summarize Ara and Brazier (2012) and TSD 12 and describe the difference between the objectives of these two studies and the objective of our estimation approach:

- Ara and Brazier (2012) propose five methods to estimate health state utility values (HSUVs) using EQ-5D data from the Health Survey of England: the additive method, the multiplicative method, the minimum method, the adjusted decrement method, and a linear regression. The authors propose four "sensitivity analyses" to compare the performance of these 5 methods: the mean absolute error (MAE), the root mean square error (RMSE), the minimum important difference (MID), and the magnitude and direction of errors across the EQ-5D range. TSD 12 is similarly focused on the question of calculating appropriate utilities for patients with comorbidities: "[…] we look at the data used to represent the HSUVs for individuals who do not have particular health conditions […], the methods used to combine HSUVs for comorbidities and the methods used to capture uncertainty in HSUVs"[1]. The appendix of TSD 12 contains a list of methods used to estimate HSUVs for comorbidities, which includes the multiplicative method.[2]
- These studies are not concerned with estimating the utilities associated with attribute impairment (as we are), but instead use existing, previously estimated, EQ-5D QALY decrements to impute the quality of life of patients living with multiple comorbid conditions. The challenge these two sources consider is a lack of quality of life data on patients living with, say, two conditions simultaneously when those data are only available for patients living with each of the two conditions separately. Our DCE exercise, on the other hand, has had to address the absence of any QALY data for the diverse attributes of a single condition, lipodystrophy, estimating these quantities from original experimental choice data.
- While use of a multiplicative method may be appropriate when combining EQ-5D QALY decrements for comorbid conditions jointly affecting individual EQ-5D domains, the distinct and previously under researched attributes of lipodystrophy are better suited to the approach we have taken, building on Viney et. al. 2014 (see below).

Question B14 also includes the comment that "[…] the other reference, Viney et al. 2014, also shows preference for a model with interaction (possibly multiplicative) rather than additive." We believe that Viney et al. (2014) actually supports the approach we have taken. Nonetheless, in response to the question, we also estimate models with interaction terms and discuss the impact their estimates are likely to have on our analysis.

[1] TSD 12, page 4

[2] TSD 12, page 28.

- The “multiplicative interaction terms” discussed in Viney et al. (2014) relate to additional terms that may be added to the right hand side of an equation that estimates the disutility associated with impairment to a vector of attributes. Consider the case of patients who only face impairment to two attributes, A and B. An estimation equation that allows for only two parameters, one for each attribute, would yield disutilities for each impairment and stipulate a linear relationship between impairment and utility.
- If, on the other hand, the analyst considers that the disutility associated with simultaneous impairment to both attributes may not be well modelled by simply adding the two decrements, they may choose to add an interaction term to the right hand side of their estimation equation. This term would allow for some non-linearity in the functional relationship between impairment and utility. Note that this relates to an exercise conducted before there are usable utility decrements, and the analyst is faced with a dataset of choices.
- The “multiplicative method” described in Ara and Brazier (2012) and TSD 12 relates to one possible way in which the utility of patients suffering from multiple conditions (the individual utilities of which are known) can be estimated. Note that this exercise presumes the existence of utilities associated with each condition. As such, the estimation of utility decrements that would have been used to calculate the condition-specific utilities is not the focus of these studies.
- In contrast, Viney et al. (2014) is in fact concerned with the estimation of utility decrements associated with specific conditions, not the evaluation of utility arising from comorbidities.
- We used Viney et al. (2014) as a guide in our econometric analysis and have adopted the simplest version of their model. However, we can also estimate the coefficients associated with interaction terms between different attribute levels:
    - Our original model allows us to estimate coefficients associated with the presence and absence of all attributes of interest, but we omit interaction terms that measure the non-additive effects of disutility from impairment to multiple attributes.
    - We can estimate a model with both main effects (those we already include) and interaction terms, as requested. In Model 2 below, the latter are included only for the most severe attribute levels, similar to Viney et al.’s (2014) approach.
    - In model 3, we include interaction terms among the attributes with the highest main effect decrements.
- Note that most coefficients in model 3 are negative, indicating that respondents perceive that the disutility from having multiple attribute impairments is higher than the sum of the individual disutilities. Importantly, by omitting these terms, our analysis may be underestimating the QALY impact of metreleptin, since treated patients experience a smaller benefit relative to SoC patients. Moreover, since we chose to implement our survey through a partial profile design (see response to question B13),

estimates of interaction terms may be subject to bias and should be interpreted with caution.[3]

Finally, while we do not feel that direct inclusion of utility losses associated with each attribute in our DCE in a multiplicative manner is consistent with the literature, we are in the process of adapting the CE to accept such values, and are also directly estimating a multiplicative utility function from the DCE data. We will provide the updated model and these results on March 2.

Supplemental material (March 2):

We have supplemented our response to question B14 by undertaking the following steps:

Step 1: Search for literature supporting a multiplicative utility model

We conducted a Google Scholar and PubMed literature search in late February 2018 using the following search terms: "multiplicative method, utility maximization," and "multiplicative method, discrete choice experiment" and "log-linear utility, discrete choice experiment" and "multiplicative discrete choice experiment utility specification" and "binary attributes in multiplicative utility functions." Additionally, in an attempt to expand the search to include relevant literature on a multiplicative estimation technique, the following search term was also used: "hedonic price estimation functional forms." The search was limited to original research both published and working papers with English abstracts. No time restriction for publication dates was used. No field restriction was placed on the publishing journal.

From this search, approximately 50 titles and abstracts were screened for relevant keywords and study applications. Studies were eligible if they used data from a discrete choice experiment, or used a multiplicative method to assess the marginal effect of attributes on the dependent variable.

After exclusion on the basis of the title and abstract, approximately 15 full papers were read and reconsidered according to the above mentioned inclusion and exclusion criteria. However, none of these 15 papers used a utility function with a multiplicative form that could be estimated without significant modification using the data collected from our DCE. In Step 2 below we propose a model to estimate appropriate multiplicative decrements, which are then implemented in the ISM.

Step 2: The multiplicative utility model

Suppose that the utility of a patient who spends T years in perfect health is $U=T*1$, and is $U(A)=T*B_i$ when that patient lives for T years with impairment to attribute i, where B_i is less than 1. More generally, suppose that **x** is a vector of indicators of impairment to n attributes.

[3] "Partial-profile CBC had some of the same weaknesses inherent to other partial-profile approachs (such as ACA): […] Reduced ability to estimate interaction effects compared to full-profile CBC (since each pair of attributes is only present in a subset of choice tasks)." (Orme and Chrzan (2017), page 91)

The patient's utility from living for *T* years with impairments characterized by **x** is the following:

$$U(\boldsymbol{x}) = T\left(\prod_{i=1}^{n} \beta_i^{x_i}\right),$$

where β_i is the **utility discount** associated with attribute *i*. Taking the *log* of both sides yields the following:

$$log\big(U(\boldsymbol{x})\big) = \log(T) + \left(\sum_{i=1}^{n} x_i log(\beta_i)\right),$$

This linear utility function can be estimated using a Multinomial Logit model, with parameters $\alpha_T, \alpha_1, \dots, \alpha_n$. Denote the estimated utility function by *V*:

$$V(\boldsymbol{x}) = \alpha_T \log(T) + \left(\sum_{i=1}^{n} \alpha_i x_i\right)$$

Notice that we can recover the original form of the equation (in which the multiple of *log(T)* is 1) by dividing all terms by α_T:

$$\frac{V(\boldsymbol{x})}{\alpha_T} = \log(T) + \left(\sum_{i=1}^{n} \frac{\alpha_i}{\alpha_T} x_i\right)$$

This implies that the estimated quantities $\frac{\alpha_i}{\alpha_T}$ correspond to the terms $log(\beta_i)$ in the expression of $log\big(U(\boldsymbol{x})\big)$ above. It follows, therefore, that $\beta_i = e^{\frac{\alpha_i}{\alpha_T}}$.

As such, in Step 3 we estimate the model using the DCE choice data and rescale its coefficients as described above in order to calculate the attribute-specific utility discount.

Step 3: Estimation of the multiplicative utility model

We consider two models that differ in the way the coefficient on the number of organs with abnormalities is estimated. Let the *"sum of organs"* variable denote the sum of organs with abnormalities presented to a respondent in a given exercise (this variable can take values between 0 and 4).

Model 1 includes the "sum of organs" variable in integer form (sum_organs2). This model assumes that the marginal effect of a change in the number of organ abnormalities on utility is constant. Namely, that the marginal disutility of an additional impaired organ is the same, regardless of the baseline number of impaired organs. Table **2** below shows that the value of this coefficient is negative and significant – impairment to an additional organ decreases respondents' utility.

Table 2: Regression Output - *Model 1*

```
Coefficients :
                   Estimate Std. Error  t-value  Pr(>|t|)
logT                0.530618   0.018944  28.0100 < 2.2e-16 ***
sum_organs2        -0.291929   0.014857 -19.6490 < 2.2e-16 ***
[remaining output omitted]
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Log-Likelihood: -7534.9
```

Model 2 replaces the sum of organs variable with indicator variables for each level of organ impairment. The reference level is set to 0, thus the estimated coefficients measure the disutility associated with each level of organ abnormality relative to no organ impairment. Table **3** below suggests that the coefficients relating to the marginal disutility of having 1, 2, or 3 organ abnormalities are negative, significant, and monotonic, so that more severe levels of impairment yield more negative coefficients. The coefficient on having 4 organ abnormalities is positive but not significant. This result is not surprising given that very few respondents were presented with choice cards that displayed hypothetical scenarios with 4 impaired organs (84 choice cards out of 28,000).

Table 3: Regression Output - *Model 2*

```
Coefficients :
                   Estimate Std. Error  t-value  Pr(>|t|)
logT                0.532831   0.019150  27.8234 < 2.2e-16 ***
num_organs1        -0.254888   0.033068  -7.7079 1.288e-14 ***
num_organs2        -0.597946   0.034593 -17.2854 < 2.2e-16 ***
num_organs3        -0.976764   0.092635 -10.5442 < 2.2e-16 ***
num_organs4        -0.166253   0.281230  -0.5912 0.5544100
[remaining output omitted]
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Log-Likelihood: -7527.9
```

Step 4: Obtaining multiplicative utility discounts from coefficients

Model 2 confirms that the marginal effect of moving across the first 4 levels of organ abnormalities (0 through 3) are similar enough such that the assumption imposed by Model 1 (that they are in fact the same) is justifiable. Thus, we use the estimated coefficients in Model 1 to calculate our multiplicative discounts. Moreover, the “constant marginal effect” assumption in *Model 1* allows us to predict the disutility associated with 4 organ abnormalities even when we rarely observe respondents making choices that involve this level of organ impairment. The estimates from *Model 1* as well as the discounts are provided in the table below:

Table 4: Multiplicative Utility Coefficients and Discounts from *Model 1*

Attribute	Coefficients	Multiplicative Utility Discounts	Significance
Log(life remaining)	0.531	1.000	1%
Sum of Organ Damaged	-0.292	0.577	1%
Amputation (e.g. toes, limb) - Present	-0.555	0.351	1%
Ability to perform work/school work - Unable	-0.614	0.314	1%
Chronic pain - Present	-0.443	0.434	1%
Depression - Present	-0.386	0.483	1%
Uncontrolled Constant Hunger (Hyperphagia) - Present	-0.386	0.483	1%
Impaired Physical Appearance - Present	-0.319	0.549	1%
Impaired Blood Sugar control - Achieved goal with Hypoglycaemia (Blood sugar excessively reduced)	-0.080	0.860	5%
Impaired Blood Sugar control - Partial Response	-0.098	0.831	5%
Impaired Blood Sugar control - No response or worsening	-0.255	0.619	1%
Loss of Response to treatment/Development of Neutralizing antibodies - Increased risk due to development of neutralizing antibodies (eg. With additional medication)	-0.343	0.524	1%
Lymphoma (A type of blood cancer) - Increased Risk	-0.282	0.588	1%
Nerve Damage (Neuropathy) - Present	-0.318	0.549	1%
Progression of Organ Impairment - Slow	-0.081	0.859	5%
Progression of Organ Impairment - Fast	-0.456	0.423	1%
Eye Damage (Retinopathy) - Present	-0.378	0.491	1%
Triglycerides (blood fat) control - Partial Response	-0.175	0.719	1%
Triglycerides (blood fat) control - No response or worsening	-0.277	0.594	1%
Disruption to female reproductive functioning - Polycystic Ovary Syndrome	-0.162	0.736	1%
Disruption to female reproductive functioning - Infertility	-0.384	0.485	1%
Log-Likelihood Ratio	-7534.872		
Mean Discount	0.594		
Variance across Discounts	0.032		

Step 5: Incorporating the multiplicative discounts into the ISM

While the proposed approach of modelling utility discounts in a multiplicative manner does mitigate the incidence of negative utility values, it raises some additional challenges. One of these is the difficulty with which expected utility calculations are made. Another is the frequency with which patients' QALYs plummet to values near zero in the presence of multiple impairments. For example, a patient with hyperphagia whose ability to work is impaired reaps 0.63 QALYs per year in the additive framework, while that same patient's utility is a little above 0.15 in the multiplicative framework.

The linear utility function used in our original submission allows us to easily calculate the expected utility of a stochastic prospect of attribute impairment. This is possible because the mathematical expectation associated with a linear utility function can be moved from outside the utility function to its argument:

$$E[U(x)] = U(E[x])$$

This property is lost when we use the proposed multiplicative utility function. Since we allow patients in the ISM to face stochastic organ impairment and incidence of hyperphagia, the multiplicative form makes expected utility more computationally demanding to calculate. To implement the multiplicative utility function in the ISM in the presence of this feature, we evaluate a patient's utility in each of the 10 possible states generated by combinations of (i) the presence and absence of hyperphagia, and (ii) the number of impaired organs. Assuming that hyperphagia (*H*) and the number of impaired organs (*N*) are the only relevant utility inputs, let U(H,N) denote utility associated with the presence or absence of hyperphagia (where *H=1* denotes the presence of hyperphagia and *H=0* the absence). Possible states are {s_{00}, s_{10}, s_{11}, s_{11}, …, s_{04}, s_{14}}, where state s_{xy} denotes the state in which the hyperphagia is determined by *H=x*, and the patient has *y* impaired organs. Let p_h denote the probability with which a patient is expected to have hyperphagia, and p_0, p_1,…, p_4 denote the probabilities with which they are expected to have 0, 1,…, 4 organs with abnormalities. Their expected utility is calculated as follows:

$$E[U(H,N)] = p_h[p_0 * U(1,0) + p_1 * U(1,1) + , \dots , + p_4 * U(1,4)] + \cdots \\ + (1 - p_h)[p_0 * U(0,0) + p_1 * U(0,1) + , \dots , + p_4 * U(0,4)]$$

Step 6: Generating ISM outputs

The ISM was adjusted to accommodate the multiplicative utility function and multiplicative discounts defined above, although we strongly caveat using these discounts in the model due to the assignment of utilities near zero for many patients. The resulting QALY benefit of treatment for the label population is 2.73, while the ICER is £2,043,742.

New sources:

Bryan Orme and Keith Chrzan (2017), "Becoming an Expert in Conjoint Analysis", Sawtooth Software Inc.

Roberta Ara and Allan Wailoo (2011), "NICE DSU Technical Support Document 12: The Use of Health State Utility Values in Decision Models", Report by the Decision Support Unit

Table 5: Additive Utility Decrement Estimation with Interactions

		Model 1				**Model 2**				**Model 3**		
		Coefficients	Decrements	Significance		Coefficients	Decrements	Significance		Coefficients	Decrements	Significance
Life remaining		0.077	1.000	1.0%		0.077	1.000	1.0%		0.068	1.000	1.0%
Life remaining x Amputation present		-0.021	-0.270	1.0%		-0.020	-0.264	1.0%		-0.013	-0.197	1.0%
Life remaining x Ability to perform work impaired		-0.020	-0.255	1.0%		-0.019	-0.252	1.0%		-0.007	-0.103	1.0%
Life remaining x Chronic pain present		-0.012	-0.153	1.0%		-0.011	-0.145	1.0%		-0.011	-0.165	1.0%
Life remaining x Depression present		-0.013	-0.175	1.0%		-0.014	-0.180	1.0%		-0.005	-0.067	10.0%
Life remaining x Heart damage present		-0.014	-0.187	1.0%		-0.015	-0.189	1.0%		-0.008	-0.113	1.0%
Life remaining x Hyperphagia		-0.009	-0.113	1.0%		-0.008	-0.105	1.0%		-0.009	-0.136	1.0%

Life remaining x Impaired physical appearance present		-0.008	-0.101	1.0%		-0.007	-0.096	1.0%		-0.009	-0.128	1.0%
Life remaining x Impaired blood sugar control at level 2		-0.005	-0.064	1.0%		-0.004	-0.058	1.0%		-0.004	-0.052	1.0%
Life remaining x Impaired blood sugar control at level 3		-0.006	-0.079	1.0%		-0.006	-0.073	1.0%		-0.006	-0.094	1.0%
Life remaining x Impaired blood sugar control at level 4		-0.014	-0.180	1.0%		-0.015	-0.194	1.0%		-0.005	-0.070	5.0%
Life remaining x Kidney damage present		-0.010	-0.128	1.0%		-0.010	-0.129	1.0%		-0.011	-0.160	1.0%
Life remaining x Liver damage present		-0.012	-0.153	1.0%		-0.011	-0.149	1.0%		-0.009	-0.137	1.0%
Life remaining x Loss of response to Treatment present		-0.011	-0.149	1.0%		-0.012	-0.154	1.0%		-0.011	-0.157	1.0%
Life remaining x Lymphoma present		-0.010	-0.132	1.0%		-0.011	-0.141	1.0%		-0.011	-0.159	1.0%
Life remaining x Neuropathy present		-0.012	-0.155	1.0%		-0.012	-0.156	1.0%		-0.014	-0.200	1.0%
Life remaining x Pancreas damage present		-0.010	-0.128	1.0%		-0.010	-0.127	1.0%		-0.012	-0.176	1.0%
Life remaining x Progression of Organ Damage present at level 2		0.002	0.032	5.0%		0.002	0.031	5.0%		0.004	0.055	1.0%
Life remaining x Progression of Organ Damage present at level 3		-0.012	-0.162	1.0%		-0.016	-0.207	1.0%		-0.009	-0.127	1.0%
Life remaining x Retinopathy present		-0.015	-0.189	1.0%		-0.014	-0.187	1.0%		-0.007	-0.109	1.0%
Life remaining x Triglycerides present at level 2		-0.004	-0.048	1.0%		-0.004	-0.046	1.0%		-0.005	-0.071	1.0%
Life remaining x Triglycerides present at level 3		-0.009	-0.112	1.0%		-0.011	-0.140	1.0%		-0.009	-0.134	1.0%
Life remaining x Disruption (to female reproductive functioning) at level 2 x Female		-0.004	-0.058	1.0%		-0.004	-0.049	1.0%		-0.005	-0.076	1.0%
Life remaining x Disruption (to female reproductive functioning) at level 3 x Female		-0.013	-0.170	1.0%		-0.014	-0.187	1.0%		-0.010	-0.150	1.0%
Life remaining x Impaired blood sugar control at level 4 x Progression of Organ Damage present at level 3						0.005	0.064	5.0%		0.009	0.132	1.0%
Life remaining x Impaired blood sugar control at level 4 x Disruption (to female reproductive functioning) at level 3 x Female						0.003	0.035			0.001	0.022	
Life remaining x Triglycerides present at level 3 x Disruption (to female reproductive functioning) at level 3 x Female						-0.001	-0.017			-0.008	-0.121	5.0%
Life remaining x Progression of Organ Damage present at level 3 x Triglyceride present at level 3						0.009	0.113	1.0%				
Life remaining x Presence of Organ Damage at level 3 x Disruption (to female reproductive functioning) at level 3 x Female						0.004	0.046					

Life remaining x Progression of Organ Damage at level 3 x Triglyceride present at level 3										0.016	0.233	1.0%
Life remaining x Amputation present x Ability to perform work impaired										-0.009	-0.139	1.0%
Life remianing x Amputation present x Depression present										-0.001	-0.008	
Life remianing x Amputation present x Heart damage present										-0.011	-0.160	1.0%
Life remianing x Amputation present x Impaired blood sugar control at level 4										-0.011	-0.167	1.0%
Life remianing x Amputation present x Progression of Organ Damage present at level 3										0.014	0.208	1.0%
Life remianing x Amputation present x Retinopathy present										-0.012	-0.182	1.0%
Life remianing x Ability to perform work impaired x Depression present										-0.013	-0.187	1.0%
Life remianing x Ability to perform work impaired x Heart damage present										-0.007	-0.109	1.0%
Life remianing x Ability to perform work impaired x Impaired blood sugar control at level 4										-0.007	-0.108	5.0%
Life remianing x Ability to perform work impaired x Progression of Organ Damage present at level 3										-0.007	-0.099	1.0%
Life remianing x Ability to perform work impaired x Retinopathy present										-0.011	-0.161	1.0%
Life remianing x Depression present x Heart damage present										0.001	0.011	
Life remianing x Depression present x Impaired blood sugar control at level 4										-0.024	-0.359	1.0%
Life remianing x Depression present x Progression of Organ Damage present at level 3										-0.016	-0.238	1.0%
Life remianing x Depression present x Retinopathy present										0.010	0.145	1.0%
Life remianing x Heart damage present x Impaired blood sugar control at level 4										-0.002	-0.029	
Life remianing x Heart damage present x Progression of Organ Damage present at level 3										-0.010	-0.142	1.0%
Life remianing x Heart damage present x Retinopathy present										-0.006	-0.082	10.0%
Life remianing x Impaired blood sugar control at level 4 x retinopathy present										-0.003	-0.044	
Life remianing x Progression of Organ Damage present at level 3 x retinopathy present										-0.007	-0.098	1.0%

Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Progression of Organ Damage present at level 3										-0.002	-0.036	
Life remianing x Amputation present x Disruption (to female reproductive functioning) at level 3 x Female										0.000	-0.003	
Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Ability to perform work impaired										0.001	0.015	
Life remianing x Depression present x Disruption (to female reproductive functioning) at level 3 x Female										0.009	0.128	1.0%
Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Heart damage present										-0.006	-0.096	10.0%
Life remianing x Disruption (to female reproductive functioning) at level 3 x Female x Retinopathy present										-0.001	-0.015	
Log-Likelihood Ratio		-7673.853				-7663.531				-7555.155		
Mean Decrement		-0.089				-0.067				-0.063		
Variance across Decrements		0.058				0.051				0.034		

Validation

B29: Priority Question: Please provide all the details of the validation exercise mentioned in Section 12.7 of the CS. Did the validation exercise include all the steps (internal validation, cross-validation, etc…) as explained for example in the AdvisHE (https://advishe.wordpress.com/) tool? If not, please include these steps as well.

Response: The validation exercise mentioned in section 12.7 specifically involved discussing the conceptual model, assumptions, and inputs with the clinical experts. Additional validation efforts were also completed, although not all types of validation were feasible due to the rare natural on lipodystrophy and lack of prior cost-effectiveness analyses. We have documented these additional efforts and limitations using the AdvisHE template [Validation.zip].

References

1. Bryan Orme and Keith Chrzan (2017), “Becoming an Expert in Conjoint Analysis”, Sawtooth Software Inc.

2. Roberta Ara and Allan Wailoo (2011), “NICE DSU Technical Support Document 12: The Use of Health State Utility Values in Decision Models”, Report by the Decision Support Uni

3. Revised Responses

Our responses to several questions have been revised to reflect corrections to the NIH Follow-Up data. These are detailed in a revised NIH Follow-Up Study summary report. Updated patient level data has been provided. [NIH Follow-Up Study_March.zip] We have additionally corrected some inconsistencies in the definition of organ abnormalities between the NIH Follow-Up Study and Natural History Study and have excluded patients with certain missing data prior to treatment from organ abnormality progression and survival analyses.

Our revised responses are presented in their entirely, along with supporting data sets and we ask that you consider these responses as replacements to our previous responses.

B3. **Priority Question:** Please provide additional description of the methodology in deriving the transition probabilities and further justification for some of the assumptions around progression of organ abnormalities.

Response:

The transition probabilities were derived separately for each observed transition (0 to 1 abnormalities, 1 to 2 abnormalities, etc) by fitting an exponential decay curve to a Kaplan Meier "survival" curve in which "survival" is defined as not developing an additional abnormality. The exercise was completed separately for each transition and each data set (NIH Follow-Up study, Natural History Study, and matched subset of Natural History Study).

The transition probabilities presented in our original submission have been recalculated to address corrections to the NIH Follow-Up study data[4] and to address inconsistencies between the definitions of heart and pancreas abnormality between the two studies. The data used in the organ progression modelling were revised to ensure consistency in the definition of pancreas damage and heart damage between treated and untreated patients (previously this analysis included both pancreatitis and diabetes as pancreas abnormalities in untreated patients and included hypertension as a heart abnormality in treated patients). Additionally, patients with later-observed organ abnormalities whose baseline status was missing were excluded from the progression modelling to avoid assuming a time of first damage when it is not known.

All data and code to replicate these analyses is provided [B3_March.zip]

[4] Corrections to the NIH Follow-Up Study data are described in the NIH Follow-Up Study summary report. Additionally, this analysis was previously completed using an older version of pancreatitis data for NIH patients and now uses the current, validated version (consistent with other analyses and the data used for the CE model).

Table 6: Baseline Summary Statistics of NIH patients and matched NHS Patients

	NIH Patients (treated)	Natural History Patients (untreated)	P-value
Age at first symptoms (mean)	13.58	14.27	0.77
Age at start of treatment (mean)	24.51	25.17	0.22
Number of impaired organs at start of treatment (mean)	2.48	2.28	0.26
GL/PL dummy (mean)	0.61	0.60	0.88
% Male	16.96	23.08	0.17
Proportion of patients with organ abnormality			
Pancreas	0.40	0.87	0.249
Heart	0.46	0.49	≤0.001
Liver	0.95	0.67	0.68
Kidney	0.66	0.31	≤0.001
Number of patients with record of blood triglyceride level	N=102	N=19	
Blood Triglyceride Level	1303.93	549.25	≤0.001

Table 7: Estimated progression probabilities - NIH Patients

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	0.0393	2	1
1 to 2	0.0555	14	4
2 to 3	0.0652	44	20
3 to 4	0.0219	52	5

Table 8: Estimated progression probabilities - Natural History Patients

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	0.0633	151	124
1 to 2	0.1063	146	96
2 to 3	0.0692	98	41
3 to 4	0.0112	41	5

Figure 1: NIH Follow-Up study organ transition Kaplan Meier curves

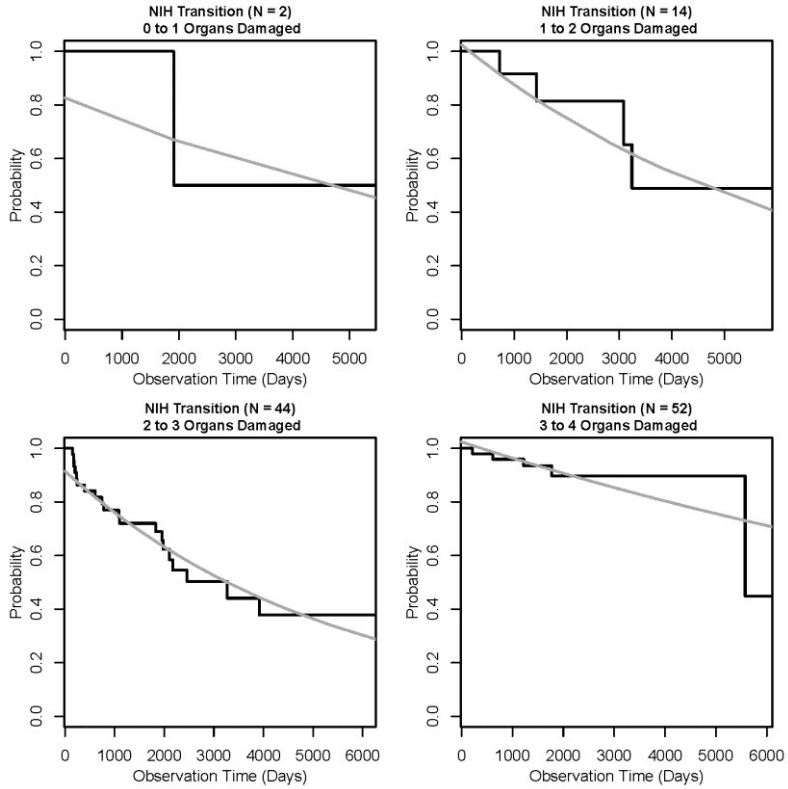


Figure 2: Matched NHS organ transition KM curves

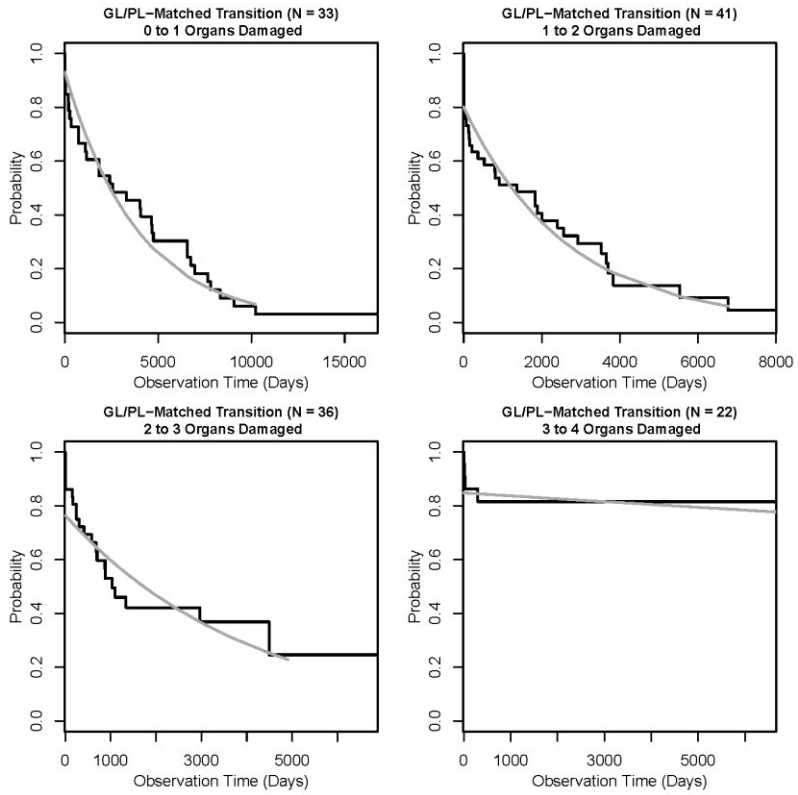


Table 9: Estimated progression probabilities - Matched Natural History Patients (using Mahalanobis matching)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	0.0896	33	33
1 to 2	0.1305	41	35
2 to 3	0.0860	36	22
3 to 4	0.0047	22	4

Table 10 and Table 11 present the statistical analyses of the transition rates. To examine whether the estimated rates were different between the NIH Follow-Up study and the Natural History Study or matched Natural History subset, we pooled the data and estimated a Cox model for each transition that related progression to an indicator for treatment (1 for patients in the NIH Follow-Up Study). To further ensure that the slower rate of progression observed in the NIH Follow-Up Study was due to fewer patients developing abnormalities and not due to censoring due to death, we also ran a collection of cox models in which the transition outcome was defined at progression or death.

Table 10: Cox Model Output Comparing NIH patients to Natural History Study patients

		Summary Statistics			Results		
Progression Event	Death Categorization	N	# Deaths	# Events	Coefficient	Hazard Ratio	Significance[1]
0 to 1	Censor	154	1	126	0.2053	1.2279	(0.774)
	Organ			127	0.6080	1.8367	(0.300)
1 to 2	Censor	164	3	103	-0.8366	0.4332	(0.033)*
	Organ			106	-0.7264	0.4836	(0.049)*
2 to 3	Censor	148	6	67	-0.1989	0.8196	(0.435)
	Organ			73	-0.2934	0.7457	(0.233)
3 to 4	Censor	100	13	11	-0.7205	0.4865	(0.248)
	Organ			24	-0.8826	0.4137	(0.041)*

Note
1. * $p<0.05$, ** $p<0.01$

Table 11: Cox Model Output Comparing NIH patients to Matched Natural History Study patients

Progression Event	Death Categorization	Summary Statistics N	# Deaths	# Events	Results Coefficient	Hazard Ratio	Significance[1]
0 to 1	Censor	37	1	36	-0.0699	0.9325	(0.924)
	Organ			37	0.3263	1.3859	(0.593)
1 to 2	Censor	60	1	43	-0.9524	0.3858	(0.021)*
	Organ			44	-0.8221	0.4395	(0.036)*
2 to 3	Censor	87	4	50	-0.3271	0.7210	(0.261)
	Organ			54	-0.3966	0.6726	(0.155)
3 to 4	Censor	83	12	9	-0.4861	0.6150	(0.498)
	Organ			21	-0.8409	0.4313	(0.079)

Note
1. * $p<0.05$, ** $p<0.01$

The treatment indicator is significant for the 1 to 2 transition and directionally correct and close to significant for the 2 to 3 transition. The 3 to 4 transition does seem to be affected by censoring and the apparent lower rate in the Natural History patients appears to be due to censoring rather than death. To account for this, we use the same transition rate for both treated and SOC patients in the CE model (2%).

Please see our response to B11 in our February 27th response for additional details regarding construction of the revised matched Natural History cohort using the Mahalanobis method.

- **(B3.a)** Please clarify why the type of affected organ (pancreas, kidney, heart and liver) and the severity of an organ abnormality (e.g. ectopic fat deposit on an organ or an organ failure) were not taken into consideration in the analysis. Based on this assumption in the CS, the cost and health outcomes from an ectopic fat deposit around the liver are the same as those from a myocardial infarction or from a kidney failure. In addition, this level of abnormality accumulation overlooks the possibility of having more than one abnormality on the same organ (e.g. fat deposit on liver in addition to cirrhosis).

Response: We recognize that a model in which we characterize a patient's disease progression by a state vector that includes information about the identity of organs with abnormalities as well as the severity of these abnormalities would be more realistic. (34-36)

There are several reasons why we have opted to use only the count of organ systems with abnormalities in the progression and survival analysis rather than a more realistic approach that accounts for the specific organ and type and severity of impairment.

1) Data constraints: our affected organ abnormality data are generated based on a single-arm trial with 112 patients, and a chart review with 178 patients. A more complex model with, say, 17 health states (combination of no, and some level of

abnormality for each of 4 organs, and death) instead of 6 would place untenable demands on the data.[5] Each patient is individually modelled as part of a cohort which evolves according to a Markov process. Increasing the number of states we specify to 17 would require estimating 256 transition probabilities, if we allow patients to transition from any state to any other state (excepting death).

2) Evidence from other CE models: While many other CE models have used larger state spaces, some CE models have found that for numerous disease states, smaller state spaces are sufficient to understand cost-effectiveness. Delea et al. estimate the cost-effectiveness of pazopanib versus sunitinib in renal cancer using a partitioned-survival analysis model with 3 health states (pre-progression, post-progression, and dead). Epstein et al. use three health states (alive, death from other causes, death from aneurysm causes) to estimate the long-term cost-effectiveness of repair options for aortic aneurysms. Clark et al. use three health states, based on degree of renal failure, to capture the cost-effectiveness of catherisation with different types of catheters.
3) Tractability of the CE model we generate: While a finer record of each patient's disease progression could provide more accurate predictions, the results we find with our existing approach allow for accommodation of our data limitations and provide sufficient validation that:
    a. The number of organs with abnormalities does have an effect on mortality (see Table 73 in the CS)
    b. Treatment does impact the rate at which patients accumulate abnormalities to their organ systems (see tables below).

    Additionally, while there are some differences in estimated utility decrements or additional costs by organ, a range of potential decrements and costs are explored in our sensitivity analysis.

Please also note that we do not claim that the number of impaired organs is the most important, or sole, indicator of disease progression. We merely argue that it is a measurable indicator that succinctly captures a patient's overall health state and provides a useful way to meaningfully estimate a treatment effect for metreleptin beyond the 15 years of data observed in the NIH Follow-Up study.

- **(B3.b)** Please provide the detailed patient level data from both the NIH Follow-Up study and GL/PL Natural History study, where the type of the afflicted organ as well as the type/severity of each observed organ impairment can be traced.

Response: Data for the Natural History Study and the NIH Follow-Up study are provided. [GL-PL-NaturalHistory.zip and NIH Follow-up Study_March.zip]

- **(B3.c)** On page 259 of the CS, above Table 71, it is explained that while the patients from the GL/PL Natural History study have data from birth, for patients in the NIH Follow-Up study, data are only available since the start of their treatment. The

[5] The 6 states in our current model correspond to (1) "alive with 1 organ abnormality", …, (4) "alive with 4 organ abnormalities", (5) "alive with no organ abnormalities", and (6) "deceased". A model in which the identity of the organ matters would include at least 17 states, since each of 4 organs would either be impaired or not (hence 24 possible states) and death. Levels for the severity of impairment would add states at an exponential rate.

submission also notes that the resulting truncated data may lead to biased estimates. Please explain the size and the direction of this bias and please justify why no attempt was made to correct for this bias?

Response: Patients with truncated histories are more likely to transition once they are observed than those patients whose prior histories are fully observed. This is because patients with truncated histories are likely to have already spent some time in the state in which they are first observed. Patients whose entire history is observed, on the other hand, spend a longer amount of time in the observed state before transitioning even if they transition at the same rate. This implies that we would estimate higher transition probabilities for those patients with truncated data (NIH patients) than those with full data (GL/PL patients).

For example, suppose that transitions are governed by an exponential decay model, which is the assumption we make when we estimate transition probabilities.[6] Under this assumption, transition to the next state depends only on the length of time a patient spends in the current state. If we observe a group of patients who had already spent some time with impairment to one organ, but whose histories we do not observe, we essentially treat them as if they have newly developed this impairment at the time they are observed.

It is clear to see that making this assumption would result in larger estimates of the transition probability than would be the case had we observed precisely when these patients develop their first organ impairment. This introduces an upward bias in our estimates of the transition probabilities for NIH patients (whose data is truncated). However, since these are the patients who benefit from the treatment under study, such a bias would make it less likely that we find a beneficial effect of the treatment. Since the bias is against the argument we seek to make in the CS, we note that our claims about the effectiveness of the treatment are conservative.

It is also important to note that the difference in observation period is not the only, or even the main, way in with the NIH Follow-Up study and the Natural History study differ. Partial lipodystrophy (PL) patients in the Natural History study were selected on the basis of medical diagnoses as reported by treating physicians during the observation period (i.e., acquired partial lipodystrophy or familial partial lipodystrophy). There was no distinction made between "severe" PL and "non-severe" PL. This created a group of patients which, as a whole, was likely less severe than PL patients at whom metreleptin treatment is targeted.

- To support this assumption, an exploratory analysis was conducted whereby PL patients from the Natural History study for whom triglycerides (TG) and/or HbA1c lab values were available at any point during the observation period were dichotomized into two subgroups of patients: one "severe" PL group (high HbA1c [≥6.5%] or high TG [≥500 mg/dL]) and one "non-severe" PL group (low HbA1c [<6.5%%] and low TG [<500 mg/dL]).

[6] In such a model, the number of patients who are yet to transition at time *t* is simply the following: $N(t)=N(0)*exp(-\lambda*t)$, where $N(0)$ is the number of patients who just transitioned into the current state.

    - Patients in the severe PL group had a higher mean number of damaged organs during the observation period than patients in the non-severe PL group (2.0 vs. 0.9, Wilcoxon rank-sum test: $p<0.001$).
    - The same trend was observed when a cut-off value of 8.0% was applied for HbA1c (2.1 vs. 1.1, Wilcoxon rank-sum test: $p<0.001$).
- Therefore, using the Natural History study as a comparator group against whom metreleptin-treated patients are compared is most likely a conservative approach.

- **(B3.d)** Please explain how to interpret the steep decline in the KM curves near t=0 in all sub-figures depicted in Figure 35, page 257 of the CS. It suggests that once a patient is being observed, 20% of patients immediately develop an organ failure, regardless of how many organs were already damaged.

Response: Since information about organ abnormalities is collected when patients make physician visits, we sometimes observe that patients are diagnosed with abnormalities to multiple organs at the same date. We deal with these cases by staggering the diagnoses so that they are one day apart. The result is that some patients seem to spend only one day in an abnormality state before transitioning to the next.

For example, a patient who is diagnosed with abnormalities to 2 additional organs, after having previously developed an abnormality to another organ will appear to have spent one day with two organ abnormalities.

The following data summarize instances in which patients included in the organ abnormality progression modelling are diagnosed with abnormalities to multiple organs on the same date:

- 14 natural history patients develop abnormalities to two organs after having had no prior abnormalities
- 9 natural history patients and 1 NIH patient develop abnormalities to two organs when they already have one afflicted organ
- 1 natural history patient develops abnormalities to two organs when they already have two other afflicted organs
- 2 natural history patients and abnormalities to 3 organs after having had no prior abnormalities
- 1 natural history patients abnormalities to 3 organs when they have previously had one afflicted organ
- 1 natural history patient develops abnormalities to all four organs at the same time

- **(B3.e)** Please justify the plausibility of the assumptions below by conducting formal statistical tests (e.g. t-test, F-test, etc.) on the available patient level data (eligible patients from the NIH Follow-Up study and GL/PL natural history study):
    - **(B3.e.1)** the probability distribution for the total number of impaired organs would follow Markov memoryless property (e.g. transition from one state to another does not depend on the time spent in the former state)

Response: We test for supporting evidence of this assumption using a linear regression framework (results presented below). We run this analysis only within our matched control cohort only as the NIH (treated) patients are observed only after starting treatment and thus a similar test on these patients would not allow us to separately identify the impact of time spent in the former state from effects of treatment by metreleptin. We do not find strong evidence that there is a consistent, significant correlation between time spent in the former state and time to progression for the matched control patients from the Natural History study (untreated).

We believe that the type of Markov process we assume above is a reasonable assumption for the purposes of the CE model. As the goal of the matching criteria is to create a control cohort that imitates the path of the NIH patients absent treatment, we argue that conditional on our matching criteria, it is unlikely that our treated patients from the NIH cohort and their matched controls from the Natural History study differ significantly in time spent in the former state for any number of impaired organs with abnormalities. Although we cannot directly test for supporting evidence of this assumption as we are unable to observe time spent in the former state for the treated NIH patients, our matching criteria (which includes age at start of treatment) balances the two cohorts in an attempt to correct for these potential systematic differences. [B3_March.zip]

Table 12: Markov Assumption Justification Analyses

	Time to Progression		
	2nd Organ	3rd Organ	4th Organ
Time Spent in Previous State	0.030 (0.042)	0.036 (0.058)	-0.125 (0.288)
Constant	1,859*** (342.4)	843.248*** (159.701)	1,733.308*** (450.106)

Full regression output are shown below:

Linear regression: Time to transition (days) from 1st to 2nd organ impairment on time to transition from 0 to 1st impairments (time_to_third_n).

```
Coefficients:
                Estimate Std. Error t value Pr(>|t|)
(Intercept)     1.859e+03  3.424e+02   5.431 4.08e-07 ***
time_to_first_n 3.025e-02  4.248e-02   0.712    0.478
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 1973 on 98 degrees of freedom
Multiple R-squared:  0.00515,    Adjusted R-squared:  -0.005002
F-statistic: 0.5073 on 1 and 98 DF,  p-value: 0.478
```

Linear regression: Time to transition (days) from 2nd to 3rd organ impairment on time to transition from 1st to 2nd impairment (time_to_third_n).

```
Coefficients:
                Estimate Std. Error t value Pr(>|t|)
(Intercept)     843.24849  159.70069   5.280 1.02e-06 ***
time_to_second_n   0.03564    0.05780   0.617    0.539
---
```

```
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 952.5 on 83 degrees of freedom
Multiple R-squared:  0.00456,    Adjusted R-squared:  -0.007433
F-statistic: 0.3802 on 1 and 83 DF,  p-value: 0.5392
```

Linear regression: Time to transition(days) from 3rd to 4th organ impairment on time to transition from 2nd to 3rd impairment (time_to_third_n).

```
Coefficients:
                Estimate Std. Error t value Pr(>|t|)
(Intercept)     1773.3075   450.1057   3.940  0.00031 ***
time_to_third_n   -0.1254     0.2879  -0.436  0.66545
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 1898 on 41 degrees of freedom
Multiple R-squared:  0.004605,   Adjusted R-squared:  -0.01967
F-statistic: 0.1897 on 1 and 41 DF,  p-value: 0.6655
```

- **(B3.e.2)** probability of developing two or more organ abnormalities in a year or improvement of the existing organ abnormalities would be always zero

Response: Although we do observe patients developing multiple organ abnormalities in a given year (approximately 64% of patients have multiple organ progressions within 1 year), we believe the assumption that only one progression can happen in a cycle is justifiable for the purposes of the CE model. This simplifying assumption would result in a conservative estimate of the benefit of metreleptin treatment. As we find that metreleptin slows organ abnormality progression, the restriction that only one organ can develop abnormalities in one cycle would underestimate the benefit of the drug as this restriction may also slow organ progression of Natural History study (control) patients.

The simplifying assumption that the probability of developing two or more organ abnormalities in a year or improvement of the existing organ abnormality is always zero allows for tractability of the CE Model.

- **(B3.e.3)** the patient characteristics such as age, gender, type of lipodystrophy, type of organ damage and severity of the abnormality, time on metreleptin treatment, blood triglyceride levels have no impact on the transition probabilities for the number of impaired organs.

Response: We acknowledge that these characteristics are important contributors to survival and progression. However, as the goal of our matching criteria is to balance several of these attributes across the NIH (treated) patients and Natural History study (control) patients, we do not anticipate that estimates derived for transition probabilities used in the CE model would be biased by systematic differences in these attributes across groups.

To examine the effect of the mentioned covariates more directly, the NIH Follow-Up data and the matched Natural History data were pooled and used in Cox models relating each transition to a indicator flagging whether a patient has been treated or not (treated), an

indicator flagging whether a patient has generalised lipodystrophy or partial lipodystrophy (gl), the age at which the patient first experiences symptoms (first_symptom_age), flag indicating whether the patients' pancreas was impaired when they were first observed (Pancreas), flag indicating whether the patients' heart was impaired when they were first observed (Heart), flag indicating whether the patients' liver was impaired when they were first observed (Liver), and a flag indicating whether the patient's kidney was impaired when they were first observed (Kidney) The patient's baseline blood triglyceride levels were not included as a covariate in the Cox models because the baseline blood triglyceride level was not available for many patients, concentrated in the Natural History study.

Although the identity of organs impaired at baseline is significant for some organs and some transitions, no consistent pattern emerges. [B3_March.zip]

Transition to 2 organ abnormality from 1 damaged organ

```
n= 50, number of events= 39
   (10 observations deleted due to missingness)

                     coef exp(coef) se(coef)      z Pr(>|z|)
treated           -0.88338   0.41339  0.80809 -1.093  0.27432
gl                 0.40560   1.50020  0.39073  1.038  0.29924
male               0.61675   1.85289  0.44102  1.398  0.16197
first_symptom_age  0.01523   1.01534  0.01461  1.042  0.29738
Pancreas0          0.30577   1.35768  0.53233  0.574  0.56569
Heart0            -1.02956   0.35716  0.42917 -2.399  0.01644 *
Liver0            -1.31301   0.26901  0.44323 -2.962  0.00305 **
Kidney0           -0.18166   0.83388  0.47903 -0.379  0.70452

Concordance= 0.738  (se = 0.056 )
Rsquare= 0.361   (max possible= 0.991 )
Likelihood ratio test= 22.36  on 8 df,   p=0.004288
Wald test            = 21.15  on 8 df,   p=0.006753
Score (logrank) test = 23.87  on 8 df,   p=0.002409
```

Transition to 3 organ abnormality from 2 damaged organs

```
n= 67, number of events= 35
   (20 observations deleted due to missingness)

                       coef  exp(coef)   se(coef)      z Pr(>|z|)
treated           -0.5457617  0.5794003  0.7291367 -0.749   0.4542
gl                -0.3195262  0.7264932  0.4310010 -0.741   0.4585
male              -0.0326239  0.9679025  0.4583078 -0.071   0.9433
first_symptom_age  0.0007565  1.0007568  0.0158095  0.048   0.9618
Pancreas0         -0.1609903  0.8513004  0.6227202 -0.259   0.7960
Heart0            -1.0335294  0.3557491  0.4681058 -2.208   0.0273 *
Liver0            -0.5505507  0.5766322  0.5112135 -1.077   0.2815
Kidney0           -0.5918481  0.5533038  0.4893926 -1.209   0.2265


Concordance= 0.688  (se = 0.056 )
Rsquare= 0.16   (max possible= 0.973 )
Likelihood ratio test= 11.68  on 8 df,   p=0.1661
Wald test            = 12.68  on 8 df,   p=0.1233
Score (logrank) test = 13.28  on 8 df,   p=0.1024
```

Transition to 4 organ abnormality from 3 damaged organs

```
n= 63, number of events= 8
   (20 observations deleted due to missingness)

                        coef  exp(coef)   se(coef)      z Pr(>|z|)
treated             1.876e+01  1.398e+08  8.218e+03  0.002    0.998
gl                 -2.403e+01  3.663e-11  8.218e+03 -0.003    0.998
male                1.873e+01  1.358e+08  8.218e+03  0.002    0.998
first_symptom_age -9.089e-02  9.131e-01  6.564e-02 -1.385    0.166
Pancreas0          -4.415e+01  6.684e-20  1.524e+04 -0.003    0.998
Heart0             -2.450e+01  2.284e-11  8.218e+03 -0.003    0.998
Liver0              2.054e+01  8.354e+08  8.218e+03  0.002    0.998
Kidney0            -2.475e+01  1.783e-11  8.218e+03 -0.003    0.998


Concordance= 0.957  (se = 0.115 )
Rsquare= 0.351   (max possible= 0.591 )
Likelihood ratio test= 27.21  on 8 df,   p=0.0006512
Wald test            = 5.23  on 8 df,   p=0.7323
Score (logrank) test = 15.22  on 8 df,   p=0.05507
```

- **(B3.f)** If possible, please provide a de-novo statistical analysis for the estimation and the extrapolation of organ abnormality progression, using common, published methods for transition probability estimation (e.g. multi-state models or maximum likelihood estimates: https://www.ncbi.nlm.nih.gov/pubmed/11788980 https://cran.r-project.org/web/packages/msm/vignettes/msm-manual.pdf), using the pooled dataset (including label-eligible patients from both NIH Follow-Up study as well as the Natural History study) [e.g. multi-state models or maximum likelihood (The statistical analysis should include all relevant covariates , where the relevance of the covariates can be determined based on properly conducted formal statistical tests, as required in the previous bullet point. Please implement the disease progression probabilities derived from this de-novo statistical analysis to the model.

Response: We would be happy to re-implement our approach using the MSM package, but having looked carefully at this request unfortunately this would not be possible for us to provide by March 2nd. Such a reimplementation could be provided with 2 weeks notice, and we await feedback from NICE as to whether this would be of interest.

B5. Please explain the improved attribute values used for metreleptin (hyperphagia, ability to work, reproduction, physical appearance and fast disease progression) in detail and provide scenarios where the baseline and follow-up attribute values are the same in both metreleptin and SoC arms.

Response: Please see the response to question B1.d for details regarding the improvement of hyperphaghia, ability to work, reproduction, and physical appearance and to questions B6 for details regarding fast disease progression. A scenario in which attribute values are the same among MET and SOC patients can be operationalized by setting all non-organ progression and lab value utility decrements to 0. Under this constraint, the model returns a QALY/ICER estimate of 3.89 /£1,434,063 for the label population.

B10: Priority Question: Please answer the queries related to the survival analyses below:

- **(B10.a)** The survival study explained in Appendix 6 includes an extrapolation exercise (17.6.2.2) for the survival of the GL/PL patients using parametric models and national life tables, followed by an estimation exercise (17.6.2.3) for the relationship between organ abnormality and mortality. While the extrapolation exercise was conducted on the patients from the NIH Follow-Up study, the estimation exercise was conducted on the patients from the GL/PL Natural History study. The hazard ratio coefficient from the estimation exercise is applied to the parametric/life table survival curves obtained from the extrapolation exercise. Please explain why the natural history dataset is used for the estimation exercise instead of NIH Follow-Up dataset.

Response: The estimation of the relationship between organ impairment and mortality was conducted using only the Natural History study both because of the data limitations of the NIH study and because metreleptin may mitigate the effect on mortality of organ abnormalities that develop prior to treatment. Since we only observe patients at the start of the trial in the NIH data, we lack information about the early stage of their disease. Moreover, the observation window in the trial is much shorter than that in the GL/PL study. A Cox proportional hazards model on the NIH study did not yield any significant results, as shown in Table 13 below. Therefore, we did not estimate the effect of organ impairment on mortality using the NIH study, and only used the Natural History study for the estimation exercise.[7]

Table 13: Cox Proportional Hazards Model of mortality on number of impaired organs using data from the NIH Study

Independent Variable	Cox Coefficient (Beta)	Exponential of Cox Coefficient (Hazard Ratio)	Standard Error (coefficient)	p-value	R2	Likelihood ratio test
FULL SAMPLE (n= 104)						
Number of Impaired Organs	0.1462	1.1575	0.2891	0.613	0.002	0.26 P = 0.6081
GL SAMPLE (n=63)						
Number of Impaired Organs	0.1199	1.1274	0.2953	0.685	0.002	0.17 P = 0.6814
PL SAMPLE (n=41)						
Number of Impaired Organs	0.6349	1.8868	1.3364	0.635	0.005	0.24 P = 0.6209

[7] One of our patients in the Natural History Study (Encrypted Patient ID: 53605772) suffered kidney impairment at birth. For this particular patient, we assumed no kidney damage in our initial analysis of the effect of organ impairment on mortality. We have since changed our approach to take this patient's impairment into account in all new analyses involving the Natural History dataset. The resulting estimate of the coefficient on organ abnormality in our Cox model is almost identical to the original estimate, hence our results are not sensitive to this change.

Full statistical outputs for the NIH study are shown below.

Cox model on full sample with 104 patients:

```
  N (Intervals) = 133, number of events= 12

             coef exp(coef) se(coef)     z Pr(>|z|)
sum_organs 0.1462    1.1575   0.2891 0.506    0.613

           exp(coef) exp(-coef) lower .95 upper .95
sum_organs     1.157     0.8639    0.6568      2.04

Concordance= 0.593  (se = 0.107 )
Rsquare= 0.002   (max possible= 0.475 )
Likelihood ratio test= 0.26  on 1 df,   p=0.6081
Wald test            = 0.26  on 1 df,   p=0.6129
Score (logrank) test = 0.26  on 1 df,   p=0.6125
```

Cox model on GL sample with 63 patients:

```
 N (Intervals) = 79, number of events= 11

             coef exp(coef) se(coef)     z Pr(>|z|)
sum_organs 0.1199    1.1274   0.2953 0.406    0.685

           exp(coef) exp(-coef) lower .95 upper .95
sum_organs     1.127      0.887     0.632     2.011

Concordance= 0.589  (se = 0.094 )
Rsquare= 0.002   (max possible= 0.63 )
Likelihood ratio test= 0.17  on 1 df,   p=0.6814
Wald test            = 0.16  on 1 df,   p=0.6848
Score (logrank) test = 0.17  on 1 df,   p=0.6845
```

Cox model on PL sample with 41 patients:

```
  N (Intervals) = 54, number of events= 1

             coef exp(coef) se(coef)     z Pr(>|z|)
sum_organs 0.6349    1.8868   1.3364 0.475    0.635

           exp(coef) exp(-coef) lower .95 upper .95
sum_organs     1.887       0.53    0.1375      25.9

Concordance= 0.647  (se = 0.275 )
Rsquare= 0.005   (max possible= 0.123 )
Likelihood ratio test= 0.24  on 1 df,   p=0.6209
Wald test            = 0.23  on 1 df,   p=0.6347
Score (logrank) test = 0.23  on 1 df,   p=0.6319
```

Data input files and code for the statistical analyses performed using the latest data are provided [B10_CoxSurvivalModel_NIHStudy_March.zip]

- **(B10.b)** Also provide de-novo extrapolation and estimation exercises, using data from a pooled dataset including label-eligible patients from both NIH Follow-Up and Natural History studies, incorporating the study ID as a separate covariate. Please implement the findings of this de-novo analysis to the model.

Response: We ran a time varying cox proportional hazard model relating mortality to number of organs with abnormalities (as well as additional covariates) on pooled data, as requested. Pooling combines all NIH and all Natural History patients. We additionally conducted a similar exercise using the matched Natural History pseudo-patients and the NIH Follow-Up study patients in which we identified a direct effect of metreleptin treatment on survival. We describe the pooled approach first, followed by the matched approach.

Our baseline model using the unmatched pooled data includes covariates such as GL/PL type, an indicator for study ID (as requested), gender, and age at the start of follow-up. We also ran a number of models to test the sensitivity of our estimates by including other covariates. See the accompanying code for details of those models, which can be readily replicated.

When the coefficient on number of organ abnormalities is used to shift the GL and PL survival curves in the CE model, the resulting ICER is £614,239/9.11 QALYs and the corresponding QALY gain is .80 (Label population, undiscounted metreleptin list price).

Data input files and code for the statistical analyses performed using the latest available data[8] are provided [B10_CoxSurvivalModel_Pooled_March.zip]

Below, we report the full statistical output from the Cox models for the unmatched, pooled analysis

---

Pooled dataset - Cox model on full sample with 282 patients, including number of organs with abnormalities (sum_organs), an indicator for PL (glplPL), an indicator for being in the NIH Follow-Up study (study_idNIH), and indicator for female (gender1), and the patients age at the start of observation (age_at_start, 0 for Natural History patients, and age at metreleptin initiation for NIH Follow-Up patients) :

```
  N (Intervals) = 547, number of events= 26

                    coef  exp(coef)   se(coef)      z Pr(>|z|)
sum_organs     7.502e-01  2.117e+00  2.135e-01  3.513 0.000443 ***
glplPL        -1.994e+00  1.361e-01  5.961e-01 -3.345 0.000823 ***
study_idNIH    1.783e+01  5.536e+07  5.508e+03  0.003 0.997417
gender1        6.631e-02  1.069e+00  4.960e-01  0.134 0.893653
age_at_start   2.680e-02  1.027e+00  2.173e-02  1.234 0.217318
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

              exp(coef) exp(-coef) lower .95 upper .95
sum_organs    2.117e+00  4.723e-01   1.39325     3.218
glplPL        1.362e-01  7.345e+00   0.04233     0.438
study_idNIH   5.536e+07  1.806e-08   0.00000       Inf
gender1       1.069e+00  9.358e-01   0.40417     2.825
age_at_start  1.027e+00  9.736e-01   0.98434     1.072

Concordance= 0.929  (se = 0.067 )
```

---

[8] After our submission to NICE in January, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017.

```
Rsquare= 0.125   (max possible= 0.347 )
Likelihood ratio test= 73.25  on 5 df,   p=2.154e-14
Wald test            = 36.09  on 5 df,   p=9.133e-07
Score (logrank) test = 93.29  on 5 df,   p=0
```

Cox model on GL sample with 119 patients including number of organs with abnormalities (sum_organs), an indicator for being in the NIH Follow-Up study (study_idNIH), and indicator for female (gender1), and the patients age at the start of observation (age_at_start, 0 for Natural History patients, and age at metreleptin initiation for NIH Follow-Up patients):

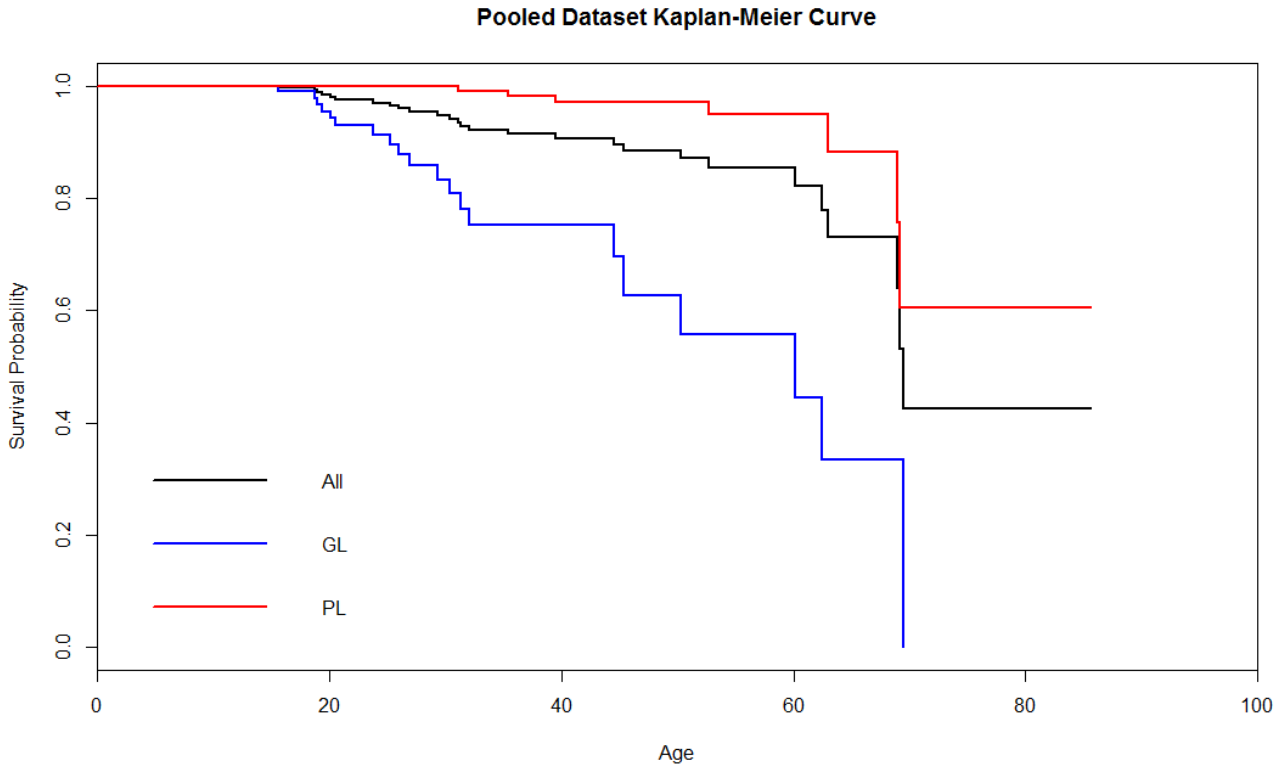
```
  N (Intervals) = 214, number of events= 19

                  coef exp(coef)  se(coef)     z Pr(>|z|)
sum_organs   4.706e-01 1.601e+00 2.265e-01 2.077   0.0378 *
study_idNIH  1.832e+01 9.059e+07 6.655e+03 0.003   0.9978
gender1      1.251e-01 1.133e+00 5.816e-01 0.215   0.8297
age_at_start 4.335e-02 1.044e+00 2.334e-02 1.857   0.0632 .
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
sum_organs   1.601e+00  6.246e-01    1.0270     2.496
study_idNIH  9.059e+07  1.104e-08    0.0000       Inf
gender1      1.133e+00  8.824e-01    0.3625     3.543
age_at_start 1.044e+00  9.576e-01    0.9976     1.093

Concordance= 0.88  (se = 0.082 )
Rsquare= 0.127   (max possible= 0.469 )
Likelihood ratio test= 29.02  on 4 df,   p=7.735e-06
Wald test            = 9.74  on 4 df,   p=0.04496
Score (logrank) test = 37.16  on 4 df,   p=1.672e-07
```

Cox model on PL sample with 163 patients including number of organs with abnormalities (sum_organs), an indicator for being in the NIH Follow-Up study (study_idNIH), and indicator for female (gender1), and the patients age at the start of observation (age_at_start, 0 for Natural History patients, and age at metreleptin initiation for NIH Follow-Up patients):

```
  N (Intervals) = 333, number of events= 7

                   coef  exp(coef)   se(coef)      z Pr(>|z|)
sum_organs    1.544e+00  4.683e+00  5.081e-01  3.038  0.00238 **
study_idNIH   1.880e+01  1.467e+08  1.394e+04  0.001  0.99892
gender1      -8.115e-01  4.442e-01  9.411e-01 -0.862  0.38853
age_at_start -8.659e-02  9.171e-01  9.053e-02 -0.956  0.33884
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

             exp(coef) exp(-coef) lower .95 upper .95
sum_organs   4.683e+00  2.136e-01   1.72975    12.676
study_idNIH  1.467e+08  6.817e-09   0.00000       Inf
gender1      4.442e-01  2.251e+00   0.07024     2.809
age_at_start 9.171e-01  1.090e+00   0.76796     1.095

Concordance= 0.924  (se = 0.145 )
Rsquare= 0.048   (max possible= 0.125 )
Likelihood ratio test= 16.42  on 4 df,   p=0.002501
Wald test            = 9.49  on 4 df,   p=0.04988
Score (logrank) test = 22.62  on 4 df,   p=0.0001509
```

Below is the KM curve (by GL/PL status) for the pooled dataset, as requested. Data input files and code is provided [B10_PooledKMCurves_March.zip]

Figure 3: Pooled data KM Curves



SURVIVAL ANALYSIS OF MATCHED DATA

In light of the revisions to the matching method and underlying data described in our responses to B3 and B11, we feel that a revision and extension of the analysis presented in Appendix 17.6.2, specifically the analysis of the direct effect of metreleptin treatment on survival using the matched Natural History Pseudo-patients pooled with NIH Follow-Up Study patients would be responsive to the question for a de novo pooled analysis. Code and associated data files are included with the materials supporting question B3 [B3_March.zip].

Figure 4 suggests a meaningful survival benefit of metreleptin, as the KM curve for the NIH patients is largely above that of the Natural History matched pseudo-patients. To identify the magnitude of the difference, a Cox proportional hazards model is estimated with a treatment dummy (that takes a value of 1 for all patients in the NIH Follow-Up study) to evaluate the effect of treatment on mortality, when the two samples are similar. Since natural history patients contribute multiple observations, standard errors at the patient level are clustered. The results are suggestive when only a treatment dummy is included, yielding a negative Cox coefficients with p-values slightly above the 0.1 threshold. The evidence for a protective effect of metreleptin treatment becomes stronger once covariates are added to the cox model to control for remaining imbalances between the samples. When indicators for

gender and type of lipodystrophy are added, the coefficient on treatment becomes significant at the p<0.05 level. The coefficients from this regression are used to derive survival curves for untreated patients from the extrapolated survival curve for treated patients (Figure 5 and Figure 6). Adding additional covariates to the cox model further strengthens the significant of the indicator for treatments and the directional effect of each covariate is sensible. As a scenario, the CE model was run using these survival curves rather than the organ abnormality specific curves with the "treated" curves applying to MET patients and the SOC curves applying to Standard of Care patients. Results were similar to the base case method, with an ICER of £670,336/QALY with 7.71 QALYs gained.

Figure 4: Cumulative survival KM curves for NIH study and matched Pseudo patients

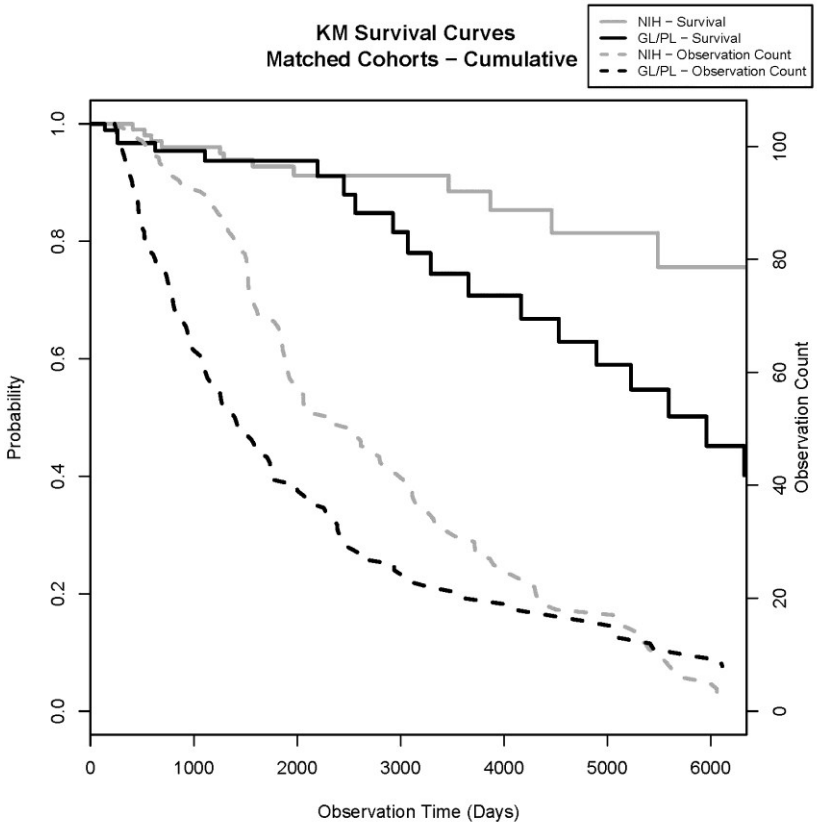


Figure 5: Treated vs. SOC patients by gender

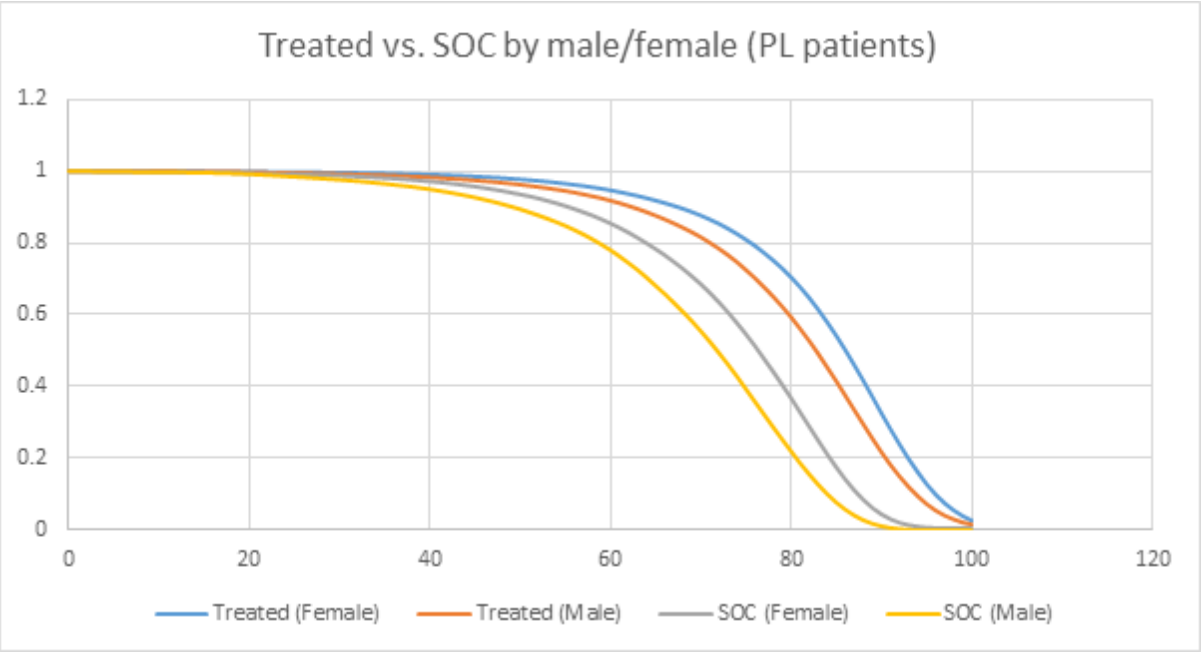
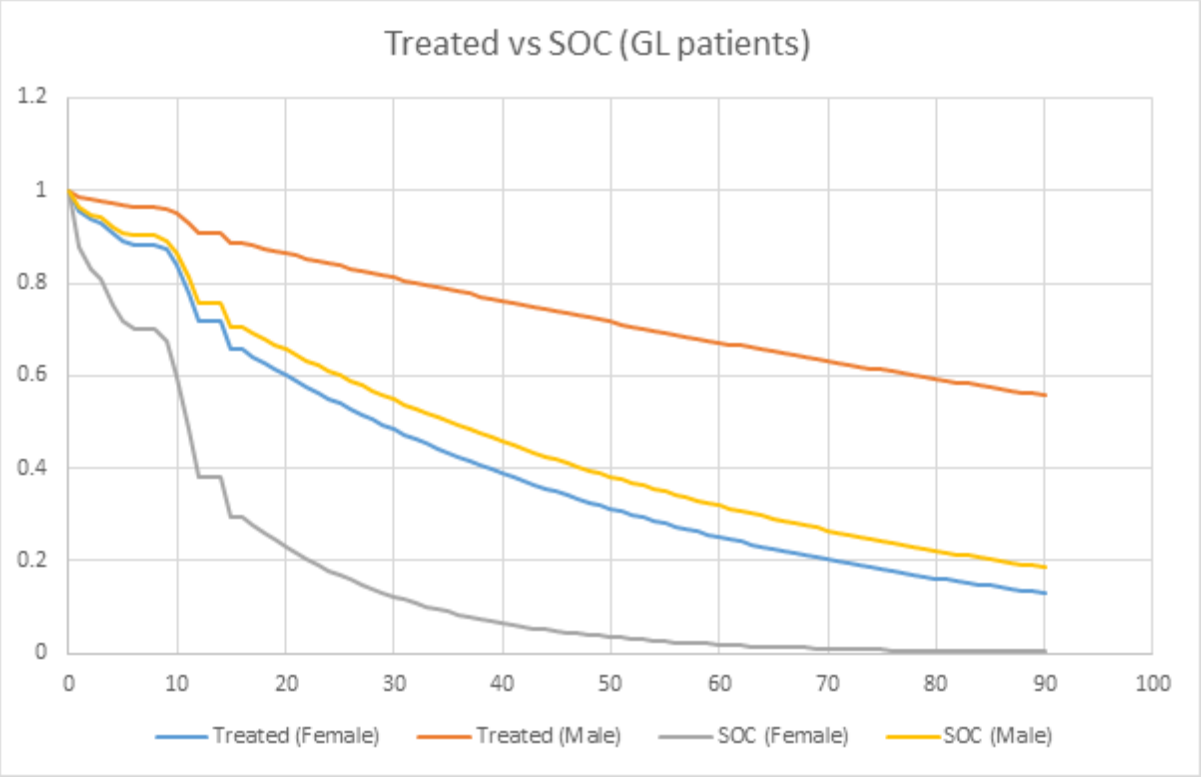


Figure 6: Treated vs. SOC patients by gender



Regression outputs

With covariates: treatment

```
n= 208, number of events= 31

          coef exp(coef) se(coef) robust se     z Pr(>|z|)
treated -0.7235    0.4850   0.3742    0.4888 -1.48    0.139

Concordance= 0.558  (se = 0.053 )
Rsquare= 0.018   (max possible= 0.721 )
Likelihood ratio test= 3.84  on 1 df,   p=0.0499
Wald test            = 2.19  on 1 df,   p=0.1388
Score (logrank) test = 3.89  on 1 df,   p=0.04846,   Robust = 1.72  p=0.1902
```

With covariates: treatment and gender

```
n= 208, number of events= 31

             coef exp(coef) se(coef) robust se      z Pr(>|z|)
treated   -0.9610    0.3825   0.3909    0.5082 -1.891   0.0586 .
maleDummy -0.8405    0.4315   0.4735    0.5742 -1.464   0.1432

Concordance= 0.58  (se = 0.058 )
Rsquare= 0.035   (max possible= 0.721 )
Likelihood ratio test= 7.31  on 2 df,   p=0.0258
Wald test            = 3.7  on 2 df,   p=0.1569
Score (logrank) test = 7.42  on 2 df,   p=0.02453,   Robust = 2.03  p=0.3616
```

With covariates: treatment, gender, and gl/pl indicator

```
n= 208, number of events= 31

             coef exp(coef) se(coef) robust se      z Pr(>|z|)
treated   -1.0582    0.3471   0.3978    0.4831 -2.190   0.0285 *
maleDummy -1.2473    0.2873   0.5051    0.6389 -1.952   0.0509 .
glDummy    1.1146    3.0483   0.5081    0.5735  1.943   0.0520 .

Concordance= 0.617  (se = 0.061 )
Rsquare= 0.061   (max possible= 0.721 )
Likelihood ratio test= 13.08  on 3 df,   p=0.004472
Wald test            = 7.37  on 3 df,   p=0.06095
Score (logrank) test = 12.92  on 3 df,   p=0.00482,   Robust = 3.37  p=0.3384
```

With covariates: treatment, gender, gl/pl indicator, and age at first symptom

```
n= 205, number of events= 29
   (3 observations deleted due to missingness)

                     coef exp(coef) se(coef) robust se      z Pr(>|z|)
treated           -1.35621   0.25763  0.41933   0.46026 -2.947  0.00321 **
maleDummy         -1.81021   0.16362  0.59171   0.58497 -3.095  0.00197 **
glDummy            0.84866   2.33652  0.61960   0.62656  1.354  0.17559
first_symptom_age -0.01991   0.98028  0.02512   0.02094 -0.951  0.34163

Concordance= 0.656  (se = 0.065 )
Rsquare= 0.086   (max possible= 0.701 )
Likelihood ratio test= 18.45  on 4 df,   p=0.001006
Wald test            = 12.95  on 4 df,   p=0.01154
Score (logrank) test = 18.07  on 4 df,   p=0.001198,   Robust = 4.5  p=0.3425
```

With covariates: treatment, gender, gl/pl indicator, age at first symptom, initial heart damage indicator, initial pancreatitis indicator, initial liver indicator, initial kidney indicator

```
n= 205, number of events= 29
   (3 observations deleted due to missingness)
```

```
                      coef exp(coef) se(coef) robust se      z Pr(>|z|)
treated           -1.94603   0.14284  0.70004   0.78868 -2.467   0.0136 *
maleDummy         -1.98290   0.13767  0.70751   0.90185 -2.199   0.0279 *
glDummy            0.82379   2.27912  0.65170   0.66816  1.233   0.2176
first_symptom_age -0.01067   0.98938  0.02591   0.02403 -0.444   0.6570
Heart              0.84415   2.32601  0.49693   0.61225  1.379   0.1680
Pancreas           0.31023   1.36373  0.53005   0.52601  0.590   0.5553
Liver              1.77286   5.88766  0.76224   1.10729  1.601   0.1094
Kidney             0.25599   1.29174  0.56885   0.50661  0.505   0.6133

Concordance= 0.723  (se = 0.065 )
Rsquare= 0.137   (max possible= 0.701 )
Likelihood ratio test= 30.1  on 8 df,   p=0.0002028
Wald test            = 19.2  on 8 df,   p=0.01385
Score (logrank) test = 27.57  on 8 df,   p=0.0005636,   Robust = 17  p=0.03014
```

- **(B10.c)** The results in Table 75 (page 266) suggests that the number of impaired organs is a significant covariate, but the ERG question if it is the only one, noting that p-values alone might not be the only decision criteria to decide on which covariates to include. Please provide all relevant details (dataset used, statistical codes compiled as well as the whole statistical outputs from the analyses including R^2 and goodness of fit results) for the survival analysis exercises conducted (base case and those in Table 75) with their explanations and provide other prognostic survival models with additional covariates (for example type of the disease, treatment received and any other relevant covariates), on the natural history dataset, NIH Follow-Up study dataset and the pooled dataset, including only label-eligible patients.

Response: In response to this request, we have estimated Cox models with additional covariates and presented the results below.

Datasets and codes for the Cox models using the Natural History Study with the original data have been provided [B10_CoxSurvivalModel_NaturalHistory.zip].
Statistical outputs for each Cox model are shown below.

Baseline model – full sample with 178 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 414, number of events= 14

    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.2839 3.6108 0.3329 3.857 0.000115 ***
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  3.611  0.2769  1.88  6.934

Concordance= 0.882 (se = 0.12 )
Rsquare= 0.05 (max possible= 0.157 )
Likelihood ratio test= 21.22 on 1 df, p=4.099e-06
Wald test   = 14.88 on 1 df, p=0.0001149
Score (logrank) test = 26.48 on 1 df, p=2.668e-07
```

Baseline model –GL sample with 56 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 135, number of events= 8

    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.0897 2.9734 0.4155 2.623 0.00873 **
```

```
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  2.973  0.3363  1.317  6.713

Concordance= 0.843 (se = 0.117 )
Rsquare= 0.069 (max possible= 0.237 )
Likelihood ratio test= 9.61 on 1 df, p=0.001935
Wald test   = 6.88 on 1 df, p=0.008725
Score (logrank) test = 11.42 on 1 df, p=0.0007247
```

Baseline model–PL sample with 122 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 279, number of events= 6

    coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.5237 4.5892 0.5302 2.874 0.00406 **
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs  4.589  0.2179  1.623  12.97

Concordance= 0.904 (se = 0.121 )
Rsquare= 0.042 (max possible= 0.116 )
Likelihood ratio test= 12.03 on 1 df, p=0.0005229
Wald test   = 8.26 on 1 df, p=0.004055
Score (logrank) test = 17.14 on 1 df, p=3.475e-05
```

Model sensitivity 1 on full sample with 178 patients including number of organs with abnormalities (sum_organs):

```
 n(intervals)= 414, number of events= 14

     coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs  3.93667 51.24774 3.68263 1.069 0.285
sum_organs_sq -0.38949 0.67740 2.01964 -0.193 0.847
sum_organs_cub -0.06185 0.94002 0.34090 -0.181 0.856

    exp(coef) exp(-coef) lower .95 upper .95
sum_organs  51.2477 0.01951 0.03758 69877.662
sum_organs_sq  0.6774 1.47623 0.01293 35.479
sum_organs_cub 0.9400 1.06381 0.48190  1.834

Concordance= 0.946 (se = 0.065 )
Rsquare= 0.101 (max possible= 0.218 )
Likelihood ratio test= 43.89 on 3 df, p=1.592e-09
Wald test   = 16.07 on 3 df, p=0.001097
Score (logrank) test = 62.73 on 3 df, p=1.532e-13
```

Model sensitivity 2 on full sample with 178 patients, including number of organs with abnormalities (sum_organs), age, indicator for female (gender1), and country (country1) :

```
 n(intervals)= 414, number of events= 14

     coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs 1.7035861 5.4936126 0.3846092 4.429 9.45e-06 ***
age   0.0004888 1.0004890 0.0228490 0.021 0.983
gender1  0.1937144 1.2137496 0.6550882 0.296 0.767
country1 -0.5334388 0.5865843 0.6808295 -0.784 0.433
---
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

   exp(coef) exp(-coef) lower .95 upper .95
sum_organs 5.4936  0.1820 2.5851 11.674
age   1.0005  0.9995 0.9567  1.046
gender1  1.2137  0.8239 0.3361  4.383
country1  0.5866  1.7048 0.1545  2.228

Concordance= 0.944 (se = 0.097 )
Rsquare= 0.091 (max possible= 0.218 )
Likelihood ratio test= 39.36 on 4 df, p=5.873e-08
```

```
Wald test   = 28.89 on 4 df, p=8.242e-06
Score (logrank) test = 60 on 4 df, p=2.908e-12
```

Model sensitivity 3 on full sample with 178 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, and leptin:

```
 n(intervals)= 414, number of events= 14

       coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs    1.873749 6.512670 0.363060 5.161 2.46e-07 ***
num_bsl_hemoglobin_a1c -0.261286 0.770061 0.432365 -0.604 0.546
num_bsl_triglycerides -0.001798 0.998204 0.001810 -0.993 0.321
num_bsl_leptin   -0.232359 0.792661 0.246952 -0.941 0.347
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    6.5127  0.1535 3.1968 13.268
num_bsl_hemoglobin_a1c 0.7701  1.2986 0.3300  1.797
num_bsl_triglycerides  0.9982  1.0018 0.9947  1.002
num_bsl_leptin   0.7927  1.2616 0.4885  1.286

Concordance= 0.941 (se = 0.091 )
Rsquare= 0.099 (max possible= 0.218 )
Likelihood ratio test= 43.09 on 4 df, p=9.9e-09
Wald test   = 28.05 on 4 df, p=1.216e-05
Score (logrank) test = 61.39 on 4 df, p=1.482e-12
```

Model sensitivity 4 on full sample with 178 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, leptin, age, indicator for female (gender1), and indicatory for country (country1):

```
 n(intervals)= 414, number of events= 14

       coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs    2.017188 7.517155 0.465604 4.332 1.47e-05 ***
num_bsl_hemoglobin_a1c -0.168343 0.845064 0.493977 -0.341 0.733
num_bsl_triglycerides -0.002167 0.997835 0.001836 -1.180 0.238
num_bsl_leptin   -0.266450 0.766094 0.266053 -1.001 0.317
age     -0.004775 0.995236 0.025004 -0.191 0.849
gender1     0.350113 1.419228 0.686823 0.510 0.610
country1    -0.742169 0.476080 0.765326 -0.970 0.332
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    7.5172  0.1330 3.0181 18.723
num_bsl_hemoglobin_a1c 0.8451  1.1833 0.3209  2.225
num_bsl_triglycerides  0.9978  1.0022 0.9943  1.001
num_bsl_leptin   0.7661  1.3053 0.4548  1.290
age      0.9952  1.0048 0.9476  1.045
gender1     1.4192  0.7046 0.3693  5.454
country1     0.4761  2.1005 0.1062  2.134

Concordance= 0.955 (se = 0.097 )
Rsquare= 0.101 (max possible= 0.218 )
Likelihood ratio test= 44.18 on 7 df, p=1.972e-07
Wald test   = 25.91 on 7 df, p=0.0005224
Score (logrank) test = 63.3 on 7 df, p=3.296e-11
```

Model sensitivity 4 on GL sample with 56 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, leptin, age, indicator for female (gender1), and indicator for country (country1):

```
 n(intervals)= 135, number of events= 8

       coef exp(coef) se(coef)  z Pr(>|z|)
```

```
sum_organs    1.871142 6.495709 0.823224 2.273 0.0230 *
num_bsl_hemoglobin_a1c -0.264345 0.767709 1.560951 -0.169 0.8655
num_bsl_triglycerides -0.006280 0.993739 0.005714 -1.099 0.2717
num_bsl_leptin    NA  NA 0.000000  NA  NA
age     -0.029539 0.970893 0.061317 -0.482 0.6300
gender1     2.327878 10.256154 1.292819 1.801 0.0718 .
country1    -3.117316 0.044276 1.659819 -1.878 0.0604 .
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    6.49571  0.1539 1.293890 32.610
num_bsl_hemoglobin_a1c 0.76771  1.3026 0.036017 16.364
num_bsl_triglycerides 0.99374  1.0063 0.982673  1.005
num_bsl_leptin    NA   NA  NA  NA
age      0.97089  1.0300 0.860950  1.095
gender1     10.25615  0.0975 0.813833 129.251
country1     0.04428 22.5857 0.001711  1.146

Concordance= 0.924 (se = 0.134 )
Rsquare= 0.117 (max possible= 0.237 )
Likelihood ratio test= 16.83 on 6 df, p=0.009948
Wald test   = 7.23 on 6 df, p=0.3005
Score (logrank) test = 15.13 on 6 df, p=0.0193
```

Model sensitivity 4 on PL sample with 122 patients including number of organs with abnormalities (sum_organs), baseline haemoglobin a1c level, triglycerides, leptin, age, indicator for female (gender1), and indicator for country (country1):

```
 n(intervals)= 279, number of events= 6

        coef exp(coef) se(coef)  z Pr(>|z|)
sum_organs    2.1243346 8.3673280 0.8921632 2.381 0.0173 *
num_bsl_hemoglobin_a1c -0.5219081 0.5933872 0.7628192 -0.684 0.4939
num_bsl_triglycerides -0.0002665 0.9997335 0.0029271 -0.091 0.9275
num_bsl_leptin   -0.2794411 0.7562062 0.3537236 -0.790 0.4295
age      0.0044091 1.0044188 0.0432232 0.102 0.9188
gender1    -0.7081594 0.4925499 1.1823639 -0.599 0.5492
country1    -0.6376429 0.5285368 1.8004896 -0.354 0.7232
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
sum_organs    8.3673  0.1195 1.45605 48.084
num_bsl_hemoglobin_a1c 0.5934  1.6852 0.13305  2.646
num_bsl_triglycerides  0.9997  1.0003 0.99401  1.005
num_bsl_leptin   0.7562  1.3224 0.37805  1.513
age      1.0044  0.9956 0.92283  1.093
gender1     0.4925  2.0303 0.04853  4.999
country1     0.5285  1.8920 0.01551 18.016

Concordance= 0.915 (se = 0.162 )
Rsquare= 0.058 (max possible= 0.116 )
Likelihood ratio test= 16.77 on 7 df, p=0.01896
Wald test   = 8.67 on 7 df, p=0.2772
Score (logrank) test = 21.29 on 7 df, p=0.003367
```

(B10.d) In the model, it is not clear why the UK life table is referred to in the end of each formula in the "SIM_Alive" sheet (from column M and onwards). Please explain.

Response: The UK life table (general population survival curve) is used for PL patients when the PL mortality benefit is switched off in the "Survival Assumptions" input tab.

- **(B10.e)** Please explain why the age of the patient is taken as an index for the PL patients survival calculations, whereas for GL patients, this index is the time from the start of the treatment?

Response: Patients with PL did not appear to experience a substantial reduction in mortality relative to the general public, on average, in the Natural History study. The UK life tables were thus used for the basis of our PL survival modelling included in the cost-effectiveness model, with increased hazard of mortality applied for PL patients with greater than average levels of organ damage. As patients with PL typically started metreleptin at later ages and thus age-related mortality becomes a relevant driver in later periods of the CE model, we chose to use age-specific mortality. For GL patients, the basis for the survival curves in the model is the treated population in the NIH Follow-Up study. Observation of these patients begins when treatment starts, and thus KM curves and survival extrapolations were conducted using the treatment start date as the index value. As GL patients experience substantial premature mortality due to their disease, and as GL patients were typically quite young when beginning treatment, disease-specific mortality (as mediated by metreleptin treatment) was chosen to drive modelled survival.

Matching:

B11. Priority Question: (B11a) Please provide all further details (datasets used, statistical codes compiled as well as the outputs of the statistical analysis) of the matching exercise in 17.6.2.4 with their explanations. Please confirm whether these analyses are in line with the NICE DSU TSD 17.

Response: Input data and code using the revised Mahalanobis method and latest data available[9] are provided as part of the data and code for question B3 [B3_ March.zip]. Please see B3 for updated matching results and our Feb 27 response for a full discussion of the matching methodology.

[9] After our submission to NICE in January, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017. Pancreatitis data have also been updated to reflect validation of pancreatitis incidence by an NIH clinician. We also corrected an inconsistency in which heart conditions were considered abnormalities in the NIH data used for this analysis relative to the definition used in the Natural history data and the definition used in the CE model. Specifically, hypertension was included as an abnormality in the previous version of this analysis. The revised data is consistent with the definition of heart abnormality used in the CE model.

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Metreleptin for treating lipodystrophy [ID861]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted]

Name of your organisation: Diabetes UK
Are you (tick all that apply):

- ✓ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

I am the nominated expert from Diabetes UK, representing clinicians in diabetes, endocrinology and metabolic medicine who might be involved in identifying patients with lipoystrophy eligible for metreleptin treatment.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None to declare**.**

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Metreleptin for treating lipodystrophy [ID861]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Lipodystrophy is a rare condition with multiple aetiologies characterised by loss of subcutaneous adipose tissue leading to absolute or relative reduction in leptin levels and development of a metabolic syndrome characterised by insulin resistance/diabetes, hypertriglyceridaemia, ectopic fat deposition e.g. in the liver, and reproductive system abnormalities.

We estimate that the number of eligible patients in England to be approximately 100 (based on a prevalence of 2 per million population as per the scope). Of this number, we estimate that up to 75% might be expected to receive treatment, hence 75 patients.

At present, most patients with this condition are referred to highly specialised units such as those at Cambridge and Oxford for evaluation and treatment. We are not aware of any significant geographic variation in practice nor of any difference in opinion between professionals involved in treating these conditions as the number of such professionals is small.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Metreleptin for treating lipodystrophy [ID861]

The current treatment for lipodystrophy involves management of the manifestations of this disease including:

- Calorie controlled, low fat diet to limit rises in triglyceride levels and to manage the consequences of the increased appetite seen with leptin deficiency
- Exercise to lower insulin resistance
- Hypolipidaemic therapies (statins, fibrates, ezetimibe, fish oils) to manage the hyperlipidaemia. Specialist medium chain fatty acid treatment for hypertriglyceridaemia.
- Diabetes medications (metformin, insulin, sulphonylureas, thiazolidinediones, DPP-IV inhibitors, SGLT-2 inhibitors) to manage the glycaemic levels and insulin resistance
- Cosmetic surgery as required
- Cardiovascular treatment (antihypertensives, percutaneous coronary intervention, coronary artery bypass) to manage heart disease
- Management of non-alcoholic fatty liver disease.

Metreleptin represents a single agent solution to many of these disease manifestations and there are no current similar alternatives to this solution. This solution is applicable, more or less equally, to the patient groups identified with this condition (despite their disparate aetiologies). We do not anticipate that the availability of Metreleptin will significantly impact the delivery of the treatment – this will continue to be a highly specialist treatment initiated and supervised by the abovementioned centres.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The Metreleptin technology being discussed here is *sui generis*. In other words, there are no current similar alternatives. With regards to starting the treatment, we anticipate that this would be restricted to properly diagnosed cases at the specialist metabolic medicine centres as noted above. The monitoring of patients on treatment would be similar to that carried out for patients who are not on treatment. Arguably, with introduction of Metreleptin treatment, the requirement for provision of other specialist services such as dietetics might be reduced. Drug burden (e.g. of hypolipidaemic or anti-diabetic drugs) could be reduced, reducing the necessity for monitoring and the likelihood of drug-related complications such as statin-induced mypopathy.

With regards to the evidence base we note that currently published trials and studies are open-label and not placebo controlled. The surrogate endpoints used in these studies (HbA1c, lipid levels, liver function tests) are reasonable and improvements in these endpoints would be expected to predict clinically important long-term impacts on future heatlh (e.g. in terms of development of cardiovascular disease, liver cirrhosis and pancreatitis). However, direct evidence of impact on clinical endpoints is lacking – given the rarity of the disease, such evidence would be hard to gather.

Adverse effects of Metreleptin recorded in trials/studies of lipodystrophic patients include:

1. Hypoglycaemia where patients are receiving insulin treatment, this would usually be managed by appropriate down-titration of treatment.
2. Injection site reactions which are usually mild.
3. Urine tract infections which would usually be managed using antibiotic therapy.
4. Anti-drug antibodies which may reduce clinical effectiveness of the medication in certain cases (doi: 10.1111/cen.12980).
5. T-cell lymphoma at a rate higher than might be expected given general population incidences (doi: 10.4158/EP11229.OR).
6. Liver and kidney adverse events (doi: 10.4158/EP11229.OR).

Long-term safety data is not generally available for Metreleptin in this patient group, although some patients have been taking this medication for up to 14 years or so. In addition, it is not clear from currently published studies that the medication remains effective in the long-term given the development of anti-drug antibodies, although there is a study that suggests that the treatment is effective over a 3-year period (doi: 10.4158/EP11229.OR).

As the studies are not placebo controlled it is not possible to say whether the adverse effects (e.g. lymphoma, liver and kidney adverse events) are definitely due to the underlying disease or due to the treatment. Given these concerns we note that Metreleptin is subject to a REMS programme in the US, and similar monitoring measures should be taken for patients given this medication in the UK. We would also be interested to know whether the abovementioned safety concerns have also been identified via the REMS programme and whether newer safety signals have also been identified, and such data should be provided by the manufacturer.

Relevant clinical guidance on the use of Metreleptin in lipoystrophy has been published by the Endocrine Society (doi:10.1210/jc.2016-2466) which was developed by a closed expert group with unrestricted educational funding from Astra Zeneca, one of the original developers of Metreleptin.

It should also be noted that Metreleptin alone and Metreleptin/Pramlintide has been trialled for treatment of non-syndromic obesity for periods of up to 6 months (doi: 10.2337/db10-1791, doi: 10.1038/oby.2009.184) and these trials did not identify any serious safety concerns.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

We are not aware of any other evidence for this technology apart from that published in the literature.

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would

any additional resources be required (for example, facilities or equipment)? Would any other specialist centre (apart from Addenbrookes) provide the technology?

NICE guidance on this technology would be useful in terms of fostering case identification and referral to specialist metabolic medicine centres for diagnosis and treatment. We do not anticipate other specialist centres apart from Cambridge or Oxford to provide the treatment. Specialist resources for diagnosis (e.g. Leptin analysis) already exist at Cambridge.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

If the NICE HST evaluation does recommend against making Metreleptin available, this could be construed as having an adverse impact on a group of people who are suffering long-term disability (a protected characteristic) from a rare and chronic disease. In addition, as many of these cases are children, there would be an adverse impact on patients of a particular age.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Metreleptin for treating lipodystrophy [ID861]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Addenbrooke's Hospital, Cambridge**

3. Job title or position	[redacted] [redacted] **National Severe Insulin Resistance Service at Addenbrooke's Hospital, Cambridge, UK**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve metabolic status and reduce long term morbidity and premature mortality in patients with lipodystrophy.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in HbA1c, fasting glucose, fasting triglycerides, reduction in % liver fat, reduction in rate of progression of liver fibrosis, improved patient quality of life, reduction in hyperphagia (excess appetite), reduction in pancreatitis, reduction in cardiovascular events and other vascular events, reduction in rate of progression of microvascular complications of diabetes (nephropathy, neuropathy, retinopathy).
9. In your view, is there an unmet need for patients and	Yes there is an unmet need as there are no other specific treatments for patients with lipodystrophy. Patients with lipodystrophy may be deficient in the appetite regulating hormone leptin and metreleptin is the only currently available treatment which can replace this deficiency.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Some patients with lipodystrophy are referred to the National Severe Insulin Resistance Service which is an NHS England funded highly specialised service based at Addenbrooke's Hospital, Cambridge. There is an baseline assessment of the patient (including leptin concentration and metabolic status), genetic testing if indicated. All patients receive specialist dietary education aiming for a low fat, low carbohydrate diet with energy balance and avoidance of weight gain in adults. In children we advise a low fat diet but aim to maintain normal growth. Insulin sensitizers (metformin), lipid lowering medication eg fibrates and diabetes treatment with oral and injectable medication are used as appropriate. Metreleptin is already currently available for selected patients via a named patient programme run by Aegerion pharmaceuticals. Some patients with lipodystrophy are not referred to the specialist service and management will vary dependent on the centre. Metreleptin therapy is only available via the service at Addenbrookes.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no current UK guidelines, but there is a wordwide multi-society guideline. J Clin Endocrinol Metab. 2016 Dec;101(12):4500-4511. Epub 2016 Oct 6. **The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline.** Brown RJ[1], Araujo-Vilar D[1], Cheung PT[1], Dunger D[1], Garg A[1], Jack M[1], Mungai L[1], Oral EA[1], Patni N[1], Rother KI[1], von Schnurbein J[1], Sorkina E[1], Stanley T[1], Vigouroux C[1], Wabitsch M[1], Williams R[1], Yorifuji T[1]
• Is the pathway of care well defined? Does it vary or are there	The pathway followed at the National Severe Insulin Resistance Service at Addenbrooke's Hospital, Cambridge, UK, is well defined for patients referred to the service. Some patients with lipodystrophy are seen in adult and paediatric Diabetes and Endocrinology centres elsewhere in the UK and as far as I know

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	the pathway of care for these patients is variable depending on the centre. Metreleptin therapy is currently only available for patients attending the specialist service in Cambridge.
• What impact would the technology have on the current pathway of care?	Metreleptin is already available for patients with lipodystrophy attending the specialist service at Addenbrooke's Hospital, Cambridge. Some patients have been treated for several years. There would be a negative impact on these patients if Metreleptin therapy was no longer available. For newly referred patients with lipodystrophy it is important that Metreleptin is available as it would improve their metabolic status, and likely also improve their prognosis. There is currently no alternative specialist medical therapy for leptin deficient patients.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, see above.
• How does healthcare resource use differ between the technology and current care?	The patients/parents of patients need to be educated on how to administer the leptin and then need 6-12 monthly follow up appointments.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	A specialist clinic already exists at Addenbrooke's Hospital, Cambridge which is set up for diagnosis, assessment, treatment and monitoring of patients with lipodystrophy and the team is already in place for teaching the patients how to use Metreleptin therapy.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In patients already taking Metreleptin therapy I anticipate that they will continue to benefit from Metreleptin therapy. For new patients we would expect to see clinically meaningful benefits in metabolic status and a reduction in long term morbidity and premature mortality from the macrovascular and microvascular complications of diabetes, episodes of pancreatitis and improvement in non- alcoholic fatty liver disease.
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or	Patients with lipodystrophy are the currently group being considered for Metreleptin therapy. This is a rare disease. The precise licenced indications are not yet available. Another potential future group of patients are the very rare patients with congenital leptin deficiency in whom leptin therapy is very effective. .

less effective (or appropriate) than the general population?	
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There are several patients who already use Metreleptin therapy and so the care pathway will not change in those patients. In new patients education on how to reconstitute and administer the Metreleptin by subcutaneous injection will be required. If patients are also taking insulin therapy they will be advised to check their blood glucose reading s regularly as a down titration of insulin therapy is usually required after Metreleptin is commenced. The patients will be reminded how to detect and treat hypoglycaemia.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We have suggested some starting/stopping rules, but this depends on the wording of the licenced indication. No additional testing would be required as patients would be seen and their metabolic status assessed regularly anyway as part of normal follow up.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I do not know what outcomes are being included in the QALY calculation but possibly reduction in hyperphagia is a benefit that may not be included.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main important side effect is hypoglycaemia which is a consequence of the metabolic effects of Metreleptin therapy. This can be avoided by a pre-emptive reduction in insulin and/or other diabetes medications at the time of the Metreleptin start and by regular blood glucose monitoring by the patient.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, but we probably also concentrate on dietary education at baseline to a greater extent than in the trials

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in HbA1c and triglycerides, reduction in liver fat. Reduction in hyperphagia. Reduction in insulin and other glucose lowering medication requirements.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes. Reduction in HbA1c has been shown to predict an improvement in long term macrovascular and microvascular outcomes in patients with diabetes in many studies (eg UKPDS/DCCT). Reduction in fasting triglycerides will predict a reduction in episodes of pancreatitis. Weight loss predicts improvement in non-alcoholic fatty liver disease.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

21. How do data on real-world experience compare with the trial data?	Patients with generalised lipodystrophy who are compliant with treatment respond very well to Metreleptin treatment as found in the trials, some being able to stop insulin therapy. Patients with partial lipodystrophy are variable in their response, factors we have found in our experience which predict a good metabolic response in partial lipodystrophy patients are a low leptin concentration pre-treatment, relatively higher HbA1c/triglycerides pre-treatment and hyperphagia pre-treatment and also good compliance with therapy.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	If the specialist centre remains only in one location in England (Cambridge) then there may be access issues for patients who live some distance from Cambridge and who are unable to afford the travel costs and/or the time needed for the travel.
23b. Consider whether these issues are different from issues with current care and why.	These issues are already in existence for current patients, but not all patients with lipodystrophy currently attend the service in Cambridge.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Metreleptin therapy effectively improves metabolic status including HbA1c and triglycerides and reduces hyperphagia in patients with lipodystrophy. Metreleptin therapy enables some patients with lipodystrophy to reduce doses or stop other glucose lowering medication eg insulin.
- Patients with generalised lipodystrophy have a more predictable positive metabolic response to Metreleptin therapy than patients with partial lipodystrophy.
- Metreleptin therapy is currently available on a named patient basis from Aegerion pharmaceuticals, but only for patients with lipodystrophy who attend the National Severe Insulin Resistance Service at Addenbrookes Hospital in Cambridge
- Metreleptin therapy should be used in combination with specialist dietary education (low fat, energy balanced dietary intake) and insulin sensitizers (metformin).
- The precise licenced indications for Metreleptin therapy are currently being considered by the EMEA and so the precise patient population to be treated is currently unclear. It is therefore not currently possible to define precise starting/stopping rules.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Metreleptin for treating lipodystrophy [ID861]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Whilst there are no guidelines as such, the majority of patients are treated at a single national expert centre (Cambridge University Hospitals NHS Foundation Trust) under the auspices of the Severe Insulin Resistant Diabetes Service. Further information can be found here: https://www.cuh.nhs.uk/addenbrookes-hospital/services/national-severe-insulin-resistance-service/national-severe-insulin-resistance-service/information-for-referring-clinicians
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across	The pathway of care to the expert centre for Severe Insulin Resistance is well-defined and set out in the NHS England service specification: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/01/a03-insulin-resist-diabetes.pdf It is however likely that a small number of patients are being managed in other centres by local experts.

the NHS? (Please state if your experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	Some patients are receiving the product on a compassionate use basis so there would be no change to their pathway of care. For new patients, they would still be seen at the single national expert centre but, as there are no other licensed treatments in the UK for generalised or partial lipodystrophy, their disease would be managed with lifestyle modifications such as: a low fat diet and exercise; cosmetic surgery; medications to manage the metabolic disturbance associated with leptin deficiency; and medications for diabetes.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	The product is only initiated at one expert centre for a small number of patients who have generalised or partial lipodystrophy.
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, the technology will be used in the same way as current compassionate use care.
• How does healthcare resource use differ	There are no other licensed treatments in the UK for generalised or partial lipodystrophy; disease is managed with lifestyle modifications such as: a low fat diet and exercise; cosmetic surgery; medications to

between the technology and current care?	manage the metabolic disturbance associated with leptin deficiency; and medications for diabetes.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should only be initiated in the single national expert centre.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment is required to introduce the technology.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	
10. What is the outcome of any evaluations or audits of the use of the technology?	The Severe Insulin Resistance service has reported that metreleptin reliably abolishes acute pancreatitis in patients with partial lipodystrophy.
Equality	

11a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
11b. Consider whether these issues are different from issues with current care and why.	Not applicable

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Metreleptin for treating lipodystrophy [ID861]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☒ a patient organisation employee or volunteer?
3. Name of your nominating organisation	Lipodystrophy UK

4. Did your nominating organisation submit a submission?	☒ no, they didn't I am the Chair of Lipodystrophy UK and was unaware that we were able to do so. Can this submission count as both since I represent the charity as well as patients?
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☒ I am drawing on others' experiences. Please specify how this information was gathered: Through our LDUK community
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition?	**Patient 1:** I was diagnosed age 50 after my daughter Addenbrooke's where very helpful and it gave answers to my body dysmorphia and escalating health problems I was previously accused of being a secret drinker because of liver changes, high blood pressure when uncontrolled caused angina.

What was the impact of this you and your family?	**Patient 2:** Ever since I can remember I have had a voracious appetite and was always hungry. I started receiving comments about my appearance from the age of 10, which have continued throughout my life. I am now 54. I first started having problems with triglyceride levels and cholesterol levels in 1999, which resulted in a hospital admission for severe right-sided pain in 1999 and an ultra sound scan showed an inflamed/fatty liver. I was eventually referred to a gastroenterologist as an outpatient and had a liver biopsy in 2000, which showed a fatty liver. I was diagnosed with alcoholic liver disease – I AM TEETOTAL. Despite repeated tests for blood alcohol levels that showed no alcohol in my system and my husband saying that I did not drink, this diagnosis was recorded in my medical records. The consultant would not listen to myself or my husband or believe the blood test results. I was discharged to my GP I was diagnosed as being diabetic in 2000 and as a result was refereed to a endocrinology/metabolic consultant who actually diagnosed me with Non-alcoholic Steatohepatitis (NASH) as my triglyceride and cholesterol levels were well above normal limits Around 25 and 44 respectively. A note was made of my muscular appearance. A combination of drugs were prescribed that had some effect on my blood lipid levels (omacor, bezafibrate and glimepiride) a statin was prescribed but I had an allergic reaction to it so it was discontinued and no alternative statin prescribed. I asked about changes to my diet and was told that "Diet made no difference at all and to just be a little careful with what I ate" I was discharged to the care of my GP with no further follow-up. My lipids were monitored by my GP but the levels were never good despite medication (ezetimbe and atorvastatin were added) resulting in episodes of pancreatitis. In 2009 my mother and family were contacted by a cousin who had been diagnosed with FPLD and was seeking more information about family medical issues. Due to a family rift many years before this was the first contact with this branch of the family. I tried to seek further information via the internet about FPLD but there was very little information, but what I gleaned pointed to the fact that all my health problems were linked to FPLD (hypertension, recurrent pancreatitis, NASH, PCOS (had hysterectomy and removal of ovaries in 2000), hypothyroidism, mixed hyperlipidaemia, diabetes). Armed with this information I tried to get my GP and consultants at my local hospital to listen and no one would.

	In August 2013 I went to my GP with a knee problem and he made note of my muscular appearance and questioned me about my family. I provided him with all the information that I had about my cousin and her diagnosis of FPLD and was referred to a diabetes consultant at my local hospital. The consultant who had seen a patient with lipodystrophy some years before, recognised my condition and made a referral to The Severe Insulin Resistance Service at Addenbrooke's Cambridge. I was seen and diagnosed with FPLD in June 2014. My lipid levels were still not good and I was asked to adhere to a 25G fat per day diet, which I did and my lipid levels improved somewhat but were still not within normal limits. Dr Stears and her team applied for Leptin on my behalf but it wasn't until August 2017 that this was approved and Leptin made available to me. Since starting Leptin my appetite has reduced, I no longer require diabetes medication and my Lipid levels have improved to within normal limits and continue to stay that way. I have always suffered with excessive tiredness, but just tried to manage this as best I could around home, work and hobbies. The delay in diagnosis and appropriate treatment has had a VERY severe impact on my life as I suffered my first heart attack at 53 in December 2016. I had no warning at all and was very fit and very active right up to this happening. An angiogram revealed that I had severe and diffuse coronary artery disease and surgery was considered to be the best option. I underwent surgery in January 2017 and due to the severe and diffuse coronary artery disease the surgery was technically difficult and challenging. During the surgery, which took 9 hours, I had 5 grafts, 2 cardiac arrests and ischemic changes to my heart, which resulted on me being placed onto ECMO (Extracorporeal Membrane Oxygenation) for 7 days and ventilated for 12 days. My family were told to expect me to die and that the only option if I did not improve was a transfer to Newcastle to have an LVAD fitted and go on the list for a heart transplant. I have recovered against all the odds and did not require an LVAD or heart transplant but have been left with severe ischaemic heart disease, unstable angina, breathlessness, nerve damage to my leg where the vein was harvested, one of my grafts has failed and 2 others are suboptimal. I had a further heart attack in August 2017 and had 4 stents fitted. I had to retire from work on ill health grounds and I will never get back to how I was before my first heart attack. I am regularly (at least once a month) blue lighted to A&E

	with chest pain not resolved with GTN spray. My husband is with me 24/7 and I don't have an independent life anymore and have had to give up my hobbies and sporting activities. **Patient 3:** I was quite fortunate in that the endocrinologist I was referred to on first experiencing health problems was familiar with Lipodystrophy and sent my bloods off for testing at Addenbrooke's. As a result, I got my diagnosis within about six months. Most patients in this community wait on average 7 years for a correct diagnosis, often with several misdiagnoses along the way.
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	**Patient 1:** Self confidence in relationship s are very much affected plus on-going fatigue and pain, which is largely unexplored by the medics. Financial impacts are travel to Addenbrooke's and self-funding some injection equipment not available on prescription. There are worries about risk of suffering or passing the gene to family. **Patient 2:** Living with FPLD is not easy as there are life style changes that need to be made to accommodate it. I worked as a theatre sister prior to diagnosis but due to the nature of my job with shifts, on call duties and working extra hours it was not easy to eat at regular times or always eat healthily as sometimes I had to eat on the hoof eating what was quick and easy not knowing when I would next get a chance to eat.. Following diagnosis and the restricted diet I was following (25G fat per day) I suffered many hypos at work and consequently I was moved to a job role that supposedly would be regular hours with no on call or shift work and the ability to eat at regular time. In reality this was far from the truth and my new job role was more pressurised than before. Even with a diagnosis of FPLD many medical professionals ignore this condition. I always carry articles about FPLD with me to give to medical professionals and I always try to explain about the FPLD but many medical professionals are still not prepared to listen e.g. In December 2016 10 days before I was diagnosed as having a heart attack, I was admitted to hospital via ambulance with chest and abdominal pain. The medical professional ignored the FPLD diagnosis and would not even consider heart issues. I was discharged home and continued to suffer for a further 10 days with chest pain when I went back to my GP who sent me straight to hospital.

	The medical profession have a tendency to look for the easiest, most simple explanation for conditions as they arise. They do look at the patient as a whole but as someone with a set of symptoms and will only deal with the ones that they specialise in. They do not listen to the patient about alternative explanations. Being diagnosed as an alcoholic when I am teetotal was very distressing and then gives other medical professionals the perfect quick ad easy solution to any new problems. Additionally the comments about my appearance over the years have affected my confidence in my appearance to the point where I always cover up i.e. long sleeves, trousers only and no skirts/dresses or shorts. **Patient 3**: Day-to-day life can be very difficult. Before leptin my biggest issue in terms of quality of life was dealing with the constant hunger. It's hard to describe if you have never experienced it but I was hungry all the time. I could eat a three-course meal and still be as hungry as if I hadn't eaten at all. I'd feel nauseated and in pain from feeling so hungry. I never felt satisfied. Being hungry all the time also means that you are thinking about food all the time. You become a little obsessed with it. And while you are always trying to fill that need for food, you inevitably don't always make the best food choices. Not good if you have a condition where you need to be careful what you eat. Following diagnosis at 17 I was started on metformin and unfortunately suffered years of severe GI upset as a result, which had a massive impact on my life, particularly as it coincided with my time at University. I was 22 by the time I developed type 2 diabetes and I started injecting insulin just a year later. It was a real shock for me; my condition was progressing more rapidly than I had expected or hoped. It was quite an adjustment to start injecting insulin and it had a massive impact on my day-to-day life. Constant injections and blood glucose checks plus all the pills to help me control high cholesterol and high blood pressure, amongst other things. As a young adult, your peers rarely appreciate your diet restrictions or a need to avoid excessive alcohol consumption! Now that my hunger levels are being managed by leptin therapy, my biggest daily challenge is fatigue. I suffer from this severely and it has a tremendous impact on my daily life. It makes it very difficult for me to

	do my job and employers only have so much patience. Once I get home from work I'm so tired I'm lucky if I have the energy to cook myself a proper meal, which inevitably impacts my ability to take care of myself properly (I live alone). It also means I have little energy for anything else and so my routine becomes a repeat of work and sleep without much time to enjoy life with family and friends. This has a knock on effect in terms of low mood and I have struggled with depression as a result. I also experience a lot of pain related to my increased muscle mass and because I cannot have help on the NHS, I've had to source a private physio for monthly sessions to ease the tension and make the pain bearable.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	**Patient 1:** Leptin has appeared to stabilise and prevent further liver damage. **Patient 2:** The care and information I receive from Addenbrooke's in Cambridge is fantastic and the team are always available to give advice/help via email or phone in between clinic appointments if required. However it takes 3.5 to 4 hours to travel to Addenbrooke's from where I live (a round trip of 7 to 8 hours). There is no care locally. Even with a diagnosis of FPLD many medical professionals ignore this condition. I always carry articles about FPLD with me to give to medical professionals and I always try to explain about the FPLD but many medical professionals are still not prepared to listen. **Patient 3:** Not only is it important to make available all suitable treatment options for all patients, one of the things missing and sorely needed is mental health care. The psychological impact of LD on patients, and their families, is huge and is so far an unmet need.
11. Is there an unmet need for patients with this condition?	**Patient 1:** There needs to be more investigation into pain **Patient 2:** There is a need for patients who have this condition to have access to local and relevant care and for Leptin to be made readily available to help them with aspects of the condition that can adversely affect their health, e.g. mixed hyperlipidaemia causing pancreatitis, heart disease, liver disease, & strokes. There is also a need to raise awareness of Lipodystrophy within the wider medical community.

	Patient 3: As described above: fatigue, pain, mental health support
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	**Patient 1:** Leptin reduces appetite, which is huge social and health problem. It is very concerning that Leptin may be withdrawn. I think more money would be spent on the severe outfall of not having leptin for example liver and heart disease. **Patient 2:** The provision of appropriate care and advice, dietary advice, and Leptin are all essential in the treatment of patients with FPLD to prevent the progression of the condition and development of associated conditions such as Diabetes, ischaemic heart disease, pancreatitis, liver disease, tiredness and excessive hunger. With earlier diagnosis and treatment with Leptin I would still be working and would have the quality of life I had before. Basically I would still be a productive and useful member of society and not the burden on society and my family that I have now become. **Patient 3:** Commencement of leptin treatment has made a big difference to my wellbeing. One of the most noticeable benefits was the change in my satiety levels. Now I can eat a modest meal and actually feel full, a new sensation for me. No more snacking all the time to fill the constant void. I can enjoy a meal and not be looking for more. Not only does this improve my quality-of-life, but it also makes it much easier for me to keep my levels under control; blood glucose, triglycerides etc. As well as the reduced food intake, the metabolic effects of leptin have made big differences. My insulin requirements have dropped by over 40%. When you are severely insulin resistant you have to inject large volumes of insulin in order to get the job done. This can be very painful and uncomfortable to do, especially when you have very little subcutaneous fat, so a reduction in insulin requirements has a big impact. The fat on my liver has dropped by almost 75%, which given the prevalence of liver disease in the LD community, is a really positive change. Leptin treatment has made a massive difference to my quality-of-life and I hope to continue to see improvements in my metabolic status. Leptin plays a big part in helping me win the battle against my condition.
13. How easy or difficult is it to take the treatment? What is the impact you and the family	**Patient 1:** Leptin is effective but having to reconstitute it with water is troublesome. Storage is also an issue regarding fridge space. **Patient 2:** I do not find the daily Leptin injections difficult. The travel to and from Addenbrooke's is exhausting and something I am not able to undertake on my

in terms or travel and receiving the treatment?	own. It takes me 2 to 3 days to recover from the journey. There is no financial help for the costs incurred and as I now have to travel to Cambridge the day before the appointment (due to the excessive tiredness I suffer from) the additional costs of accommodation and meals have to be met by myself. Even when I was still working I had to use annual leave days to go to these appointments as there was no alternative for the time off and my employers were not accommodating regarding this. I used to work for the NHS **Patient 3:** Since I was already injecting insulin, the twice-daily injections were not new to me, and this certainly helped! There is a lot of paraphernalia that comes alongside leptin administration, as the powdered drug needs to be reconstituted before it can be injected. This is mainly an issue when travelling as sometimes half my case can be taken up with all my medication and the associated equipment.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	**Patient 1:** I don't see a problem with technology; Leptin and high dose insulin in a pen form would be more convenient **Patient 2:** No comments **Patient 3:** I have experienced no adverse side effects. Leptin injections are less painful than insulin injections. This treatment does not help with fatigue or pain (other than hunger pains).

Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	**Patient 1:** No comments **Patient 2:** No comments **Patient 3:** All lipodystrophy patients with low leptin levels would benefit from this treatment.
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**Patient 1:** Patients unable to access Addenbrooke's whether financial or health restrictions are at a disadvantage **Patient 2:** No comments **Patient 3:** Travel to and from Addenbrooke's, as it is the only National Centre of Excellence for Lipodystrophy. It can be very time-consuming and expensive to attend.
Other issues	
17. Are there any other issues that you would like the committee to consider?	**Patient 1:** No **Patient 2:** No comments **Patient 3:** Patients are living with this condition long-term and so there is a long time for the condition and associated complications to develop. We need to take preventative action as early as possible. This is the first opportunity our community has had of receiving a treatment that is specifically used to at least partly remedy the effects of lipodystrophy, instead of managing the secondary consequences.
Key messages	
18. In up to 5 bullet points, please summarise the key messages of your statement:	

- Huge negative impact of hyperphagia on quality of life
- Lack of alternative treatments
- Positive impact of treatment on metabolic profile
- Psychological benefits of treatment options

Thank you for your time.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Metreleptin for treating lipodystrophy [ID861]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):

3. Name of your nominating organisation	Lipodystrophy UK
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: My mum has been taking Leptin therapy for about 2 years and we discuss our condition and treatment often.
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition? What was the impact of this you and your family?	I was diagnosed in February 2008. I had been in Plymouth University and being treated for my diabetes at Derriford hospital. Addenbrooke's Hospital and the WELLCOME centre sent a request for patient information of any patients fitting diagnostic criteria that I met. I was asked if I consented to blood samples and data being sent as part of the study, which I did. After having forgotten about the study I was called by Dr David Savage from Addenbrooke's to tell me they found a genetic mutation. Having had dental surgery under sedation the previous day, I remembered very little of what I was told. I was asked to have a DEXA scan and this was arranged to be done in Plymouth (though I had moved to Bristol). It got cancelled a couple times. I was then invited to visit the Wellcome centre in Addenbrooke's for a number of tests. As I was one of the earlier people to be diagnosed with my specific mutation, the delay in diagnosis didn't really impact me or my family directly.

9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in school and social life. What is the effect on any siblings?	Living with the condition seems to present an increasing amount of challenges. At the time of diagnosis, I was working full time, though regularly being called up for poor attendance. While my understanding of equality law meant that I was able to avoid dismissal, I was pushed towards resignation or going part time. I am no longer able to work due to fatigue and chronic pain. I didn't return to work after having my daughter in 2012. I worked part time for about 6 months in 2015 but between personal circumstances and my health and poor attendance I felt cornered into a resignation. I am now on the support group of Employment Allowance. I find my physical health stopping me from working has a negative impact on my mental health. I feel guilt and I feel my mind is being wasted. Not being able to work has a major financial impact in itself. While I was working I was held back from promotions and pay rises. My health was a part of the breakdown of my marriage. My ex-husband didn't appear to make any attempt to understand my condition. He became resentful of me not working and told me I was "hiding" behind my health and condition as an excuse. My current partner is more understanding but does have occasional moments of lacking empathy. Friendships can be hard to maintain when I have to cancel plans last minute or I have to end an evening early. My social life is very limited, pain and fatigue flares mixed with having a small child mean that I struggle to plan meeting up with friends. I have been confronted by friends accusing me of avoiding them. There are group things that I know I wouldn't be able to join in with, like bike rides and walking days. I feel like I miss out. My appearance is also a major issue for me. I often feel self-conscious, not helped by strangers asking about my xanthomas or asking when my non-existent baby is due. But then I also have people who joke they wish they could have my condition. I find getting well-fitting clothes is difficult. At the moment I live in a terraced house, stairs are a challenge at times. I have handles in the bathroom to help get up from the loo and bath.

Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	As there is currently only one specialist clinic in Addenbrooke's Hopital, this makes accessing knowledge and treatments for the complications very difficult. The treatments on the NHS are currently only to "firefight" the array of symptoms. I am under multiple specialists at local clinics and I seem to acquire more and more of them as I go. Each specialist only treats their own "bit" There is minimal holistic treatment for the umbrella condition. There doesn't even seem to be much communication between doctors, no multi-disciplinary team. The burden of communication falls to me, the patient.
11. Is there an unmet need for patients with this condition?	There is huge unmet need for patients with all forms of Lipodystrophy in both understanding of the condition and treatment options.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also	The main advantage for the treatment for me is the reduction in appetite. A reduction in appetite has a domino effect by feeling less need to constantly eat my hba1c and triglyceride readings are improved. I feel less tortured by a lack satiety. While it seems bizarre to many, the ability to feel full after a meal or even part way through a meal is a complete revelation to me. It has a highly positive impact on my mental health, feeling "normal" in that aspect. Before leptin treatment I don't feel that I would have been able to drop my carbohydrate intake from my diet as much as I have now.

include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends and participate in school and social life.	
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	I needed to purchase a small separate fridge to store the medication and making up the vials every other day can be tedious. When travelling I have to consider the availability of cold storage and transporting needles. It doesn't have any major impact, just takes a little more planning. Reconstituting the powder form it comes in can feel tedious if I am tired. The actual injection is easy if at home.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they	The main disadvantage is the need for refrigeration, It means extra planning for any travel and the storing it takes up space. The only other disadvantage I can think of is injecting with a syringein the abdominal area subcutaneously can be painful. This is because of the lack of fatty tissue. If I accidentally strike a muscle then it is like a bee sting.

long term or short term and what impact do they have? Are there any aspects of the condition that the treatment does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	I only know from speaking to other patients and sharing anecdotes that this treatment does not benefit everyone equally, as with any treatment.
Equality	
16. Are there any potential equality issues that should be taken into account when	

considering this condition and the treatment?	
Other issues	
17. Are there any other issues that you would like the committee to consider?	
Key messages	

18. In up to 5 bullet points, please summarise the key messages of your statement:

- Familial Partial Lipodystrophy has a major impact on far reaching different aspects of life
- There is major lack of understanding of the condition in the general medical community
- Leptin replacement therapy is one of the only options available
- The impact of controlling insatiable hunger should not be underestimated in terms of both physical and mental health
-

Thank you for your time.

in collaboration with:

Erasmus School of Health Policy & Management

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Metreleptin for treating lipodystrophy

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Marie Westwood acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nasuh Büyükkaramikli acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Isaac Corro Ramos, Marscha Holleman and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Regina Leadley and Rob Riemsma acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance on the health economics part of the project. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	antidrug antibodies
AE	Adverse Events
AGL	acquired generalised lipodystrophy
ALT	alanine aminotransferase
APL	acquired partial lipodystrophy
AST	aspartate aminotransferase
BI	budget impact
BIC	Bayesian information criterion
BMI	body mass index
BSCL	Berardinelli-Seip congenital lipodystrophy
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CFAS	controlled concomitant medication full analysis set
CGL	congenital generalised lipodystrophy
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CUH	Cambridge University Hospitals
DCE	Discrete choice experiment
DM	diabetes mellitus
EAP	early access programme
EMA	European Medicines Agency
EMR	electronic medical record
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESRD	end-stage renal disease
EUR	Erasmus University Rotterdam
FAS	full analysis set
FDA	Food and Drug Administration
FFA	free fatty acid
FPL	familial partial lipodystrophy
GI	gastrointestinal
GL	generalised lipodystrophy
GPRD	General Practice Research Database
HbA_{1c}	glycated haemoglobin
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
HRG	Healthcare resource groups
HRQoL	Health-related quality of life
HST	Highly specialised technologies
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio

ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LD	lipodystrophy
LDL-C	low density lipoprotein cholesterol
LOCF	Last observation carried forward
LS	least squares
LYG	Life year gained
LYS	Life year saved
MAA	marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	mixed-effect model repeated measures
MPGN	membranoproliferative glomerulonephritis
MRU	Medical resource utilisation
NA	Not applicable
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
PCOS	polycystic ovary syndrome
PL	partial lipodystrophy
PRESS	Peer review of electronic search strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY(s)	Quality-adjusted Life Year(s)
QoL	quality of life
RCT	Randomised controlled trial
REMS	Risk evaluation management strategy
SAS	safety analysis set
SAE	Serious Adverse Events
SC	subcutaneous
SD	Standard deviation
SEM	standard error on the mean
SmPC	Summary of product characteristics
SoC	Standard of care
TEAEs	Treatment-emergent adverse events
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
ULN	upper limit of normal
USA	United States of America

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1. SUMMARY

1.1 Background

The term lipodystrophy describes a heterogeneous group of rare disorders, which are characterised by a deficiency of adipose tissue (body fat) without underlying nutritional deprivation. Lipodystrophy syndromes are associated metabolic abnormalities, including diabetes mellitus (DM), hypertriglyceridemia and steatohepatitis, and with organ damage consequent upon ectopic lipid storage.

Lipodystrophy syndromes are categorised by aetiology (genetic or acquired) and by the distribution of adipose tissue deficiency (generalised, affecting the entire body, or partial). This results in four major categories: congenital generalised lipodystrophy (CGL), acquired generalised lipodystrophy (AGL), familial partial lipodystrophy (FPL) and acquired partial lipodystrophy (APL).

Congenital generalised lipodystrophy, also known as Berardinelli-Seip syndrome, is an autosomal recessive disorder with multiple genetic causes, which is characterised by an almost complete lack of body fat and prominent muscularity starting at birth or in infancy. Soon after birth, patients with CGL exhibit insatiable hunger and accelerated linear growth rates. Infants may also develop hepatosplenomegaly and umbilical prominence or hernia. Additionally, patients may have phlebomegaly and acanthosis nigricans later in childhood. Acquired generalised lipodystrophy, also known as Lawrence syndrome, is more common in females (female:male ratio 3:1) and appears usually before adolescence (but may develop at any time in life) with progressive loss of fat affecting the whole body including palms and soles of the feet. Familial partial lipodystrophy is a group of extremely rare, usually autosomal dominant disorders, characterised by loss of fat affecting the limbs, buttocks and hips. Patients also have fat accumulation in the face, neck, and intra-abdominal areas, causing a Cushingoid appearance. Acquired partial lipodystrophy, also known as Barraquer-Simons syndrome, usually has a childhood or adolescent onset and is more common in females (female:male ratio 4-5:1). APL is distinguishable from other lipodystrophy (LD) syndromes by the unique cephalocaudal progression of subcutaneous fat loss that is observed. Subcutaneous adipose tissue loss begins in the face and subsequently spreads to the neck, upper extremities, thorax and abdomen.

1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology

The company submission (CS) states that interviews with patients with lipodystrophy were conducted, at the US National Institutes of Health, on behalf of Aegerion, and that these interviews demonstrate the negative impact of lipodystrophy. This interview study is referenced as: 'Agerion Pharmaceuticals Ltd. Lipodystrophy patient research (NIH). Data on file. 2017.' Neither these data, nor a description of the interview study, were provided.

The CS includes the following statements, summarising the findings of the interview study:

- Patients are highly constrained by food access issues, impacting on many aspects of their daily lives including attending school, work and social situations. Patients also

suffer from mood and sleeping problems. The extreme level of food seeking additionally creates stress on families/carers. Carers may need to provide 24/7 supervision, especially as patients may also consume inappropriate or non-food items.

- Female lipodystrophy patients can suffer reproductive dysfunction as a result of leptin deficiency and severe insulin resistance. The adverse impact of reproductive dysfunction in females in the general population, including polycystic ovary syndrome (PCOS), infertility and miscarriage are well documented. For example, the spectrum of the symptoms of PCOS such as hirsutism, skin problems, menstrual problems and finally infertility has a huge negative impact on the individuals' psychological and interpersonal functioning. The interviews with patients with lipodystrophy confirm the impact of reproductive dysfunction in the context of lipodystrophy.
- Patients with LD can experience anxiety and depression due to the clinical burden of the disease including impaired physical appearance (which can be associated with bullying and low self-esteem), hyperphagia, reproductive dysfunction, fatigue and chronic pain.
- Other symptoms such as fatigue and frequent infection/illness, in addition to hyperphagia and anxiety/depression, can lead to impaired or complete inability to work or attend school, as well as to social isolation. In turn members of the family may not be able to work or socialise due to caring responsibilities.

The CS (pages 44-48) presents selected quotes from patients with lipodystrophy and their carers, in support of the above points.

The CS also states that: 'Metreleptin treatment is effective at improving metabolic abnormalities associated with LD, both in the short-term and long-term. Many of these changes have the potential to substantially improve the QoL of patients and their carers.'

1.3 Critique of the decision problem in the company's submission

The remit of this appraisal, as defined in the final agreed NICE scope, is to evaluate the benefits and costs of metreleptin within its licensed indication for treating lipodystrophy for national commissioning by NHS England.

At the time of submission of the ERG report, metreleptin did not have a marketing authorisation in the UK for the treatment of lipodystrophy. The latest available information (09/03/2018) is that:

[redacted]

[redacted]

The ERG notes some deviations from the final agreed NICE scope. Briefly, these include:

- The CS (section 12.1.2, page 153) states that the comparator for the cost effectiveness analysis was standard clinical management without metreleptin, as defined in the NICE scope, (including lifestyle modifications such as diet and exercise, use of lipid lowering drugs; and medications for diabetes). However, no data for the comparator were included in the clinical effectiveness section of the CS.
- The clinical effectiveness section of the CS focuses primarily on metabolic outcome measures; the CS includes no data or only very limited data for the clinical or patient-perceived outcomes specified in the NICE scope. No data are provided on liver cirrhosis, complications of diabetes, organ damage (including heart and kidneys) or effects on appearance. Mortality and pancreatitis are only reported where these are considered to be adverse effects of treatment or, in the case of pancreatitis, discontinuation of treatment.

The ERG recognises that no comparative studies of metreleptin versus standard care are available and that, in such cases, cost effectiveness analysis requires an indirect comparison between treatment and comparator studies. However, where indirect comparisons are used, it is essential that the same rigorous approach to identifying, selecting and reporting studies is applied for both intervention and comparator studies. There are serious problems with the identification, selection and reporting of comparator data in the CS. No systematic attempts to identify comparator studies and no selection criteria for such studies are reported. Parameters for the standard of care arm, in the cost effectiveness analysis, were informed by a single natural history study, which was not included in the CS.

The ERG has extracted additional data on clinical/patient-perceived outcomes from a short report of a follow-up study to the main study included in the CS, which was provided in response to clarification questions. This study was used in the cost effectiveness analyses, but was not included in the clinical effectiveness section of the CS.

1.4 Summary of clinical effectiveness evidence submitted by the company

Single arm, observational studies of metreleptin treatment found improvements in metabolic abnormalities from baseline to month 12 of treatment in patients with GL and in the subgroup of patients with PL who had similar metabolic disturbances to those seen in patients with GL (PL patients with leptin level <12 ng/ml with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L).

- In study NIH 991265/20010769, mean actual change in HbA_{1c} to Month 12/LOCF was -2.2% (95% CI: -2.7 to -1.6, p<0.001) for GL patients and -0.9% (95% CI: -1.4 to -0.4, p<0.001) for patients in the PL subgroup.
- In study FHA101, mean actual change from baseline to Month 12/LOCF for HbA_{1c} was -1.2% (95% CI: -4.3 to 2.0) for GL patients and -0.9% (95% CI: 95% CI: -1.4 to -0.4) for patients in the PL subgroup.

- In study NIH 991265/20010769, mean percent change in triglycerides to Month 12/LOCF was -32.1% (95% CI: -51.0 to -13.2, p=0.001) for the GL group and -37.4% (95% CI: -57.2 to -8.6, p<0.001) in the PL subgroup excluding the one outlying noncompliant patient.
- In study FHA101, mean percent change from baseline to Month 12/LOCF for triglycerides was similar in the GL group as -26.9% (95% CI: -124.1 to 70.4); however, for the PL subgroup, the mean percent change was lower at -8.5%. (95% CI: -36.4 to 19.5) Five of the seven patients in the PL subgroup in this study showed reductions from baseline to Month 12/LOCF in triglycerides ranging from -5.7% to -52.3%.
- Mixed model repeated measures (MMRM) analyses, from study NIH 991265/20010769, indicate that these effects persist to month 36.

With respect to safety and adverse events, the CS concludes that the known side effects of metreleptin can be managed as part of the normal clinical practice for patients with this complex condition. The ERG notes that the CS does not report the safety concerns as highlighted in the Centre for Drug Evaluation and Research Report (not included in the CS) nor the associated risk evaluation management strategy (REMS). The summary of safety in this report states: 'The principal safety concerns with metreleptin are T-cell lymphoma and anti-metreleptin antibodies with neutralizing activity. These concerns are of sufficient magnitude to require REMS. Other safety findings that warrant inclusion in the Warning and Precautions section of the metreleptin labelling include hypoglycemia, autoimmunity, and hypersensitivity.'

The clinical effectiveness sections of the CS did not include any results from control/comparator studies.

1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. The CS states that a SLR was conducted to search for trials of metreleptin and trials of relevant comparators. However, the ERG is concerned that the search strategies did not contain any terms for comparators and only studies for the intervention will have been retrieved.

The key issue limiting the robustness of the efficacy data presented in the CS is the lack of any comparative studies; estimates of treatment effects are based on changes from baseline in single arm metreleptin treatment studies. This problem is compounded as the CS does not include any attempt to draw indirect comparisons through studies of the effects of established clinical management (diet, lifestyle modifications, lipid lowering drugs and anti-diabetic medications). The natural history study, used to provide comparator data for the cost effectiveness analysis, is not included in the clinical effectiveness sections of the CS and has a population which is not comparable to those included in the metreleptin intervention studies.

A further substantive issue concerns the nature of the treatment effects reported. The CS focuses primarily on changes in surrogate outcome measures (e.g. HbA_{1c}, triglycerides, hepatic enzymes) and includes very little information about any effects of treatment on patient-

perceived symptoms and clinical outcomes (e.g. hyperphagia, organ damage). Further data were available from a follow-up study, which was used in cost effectiveness modelling, but was not reported in the clinical effectiveness sections of the CS.

1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The CS states that a systematic review was undertaken for economic, cost and resource use and health-related quality of life (HRQoL) evidence using a combined search for all of these areas. The cost effectiveness searches in the company submission were reported in enough detail for the ERG to appraise them. Three economic evaluation studies were identified by the company. However, none of these studies were eligible for inclusion in the review of economic evaluations of metreleptin, since the scope of all studies was not relevant to the CS.

A patient-level model was developed, aiming to assess the cost effectiveness of metreleptin versus standard of care (SoC) for patients with lipodystrophy. The model had a cycle length of one year and a time horizon of 60 years. A UK NHS PSS perspective was used in the model. Base case outcomes were incremental costs per quality-adjusted life-year (QALY) gained for metreleptin compared to standard of care. Both costs and effects are discounted at rate of 3.5%.

Two identical cohorts with 112 patients were used to populate the model. Individual patient data was obtained from the NIH follow-up study. Where individual patient data were not available, a Markov approach was used. A patient's survival probability is affected by abnormalities in a patient's heart, liver, kidney, or pancreas, i.e., the more organs with abnormalities, the higher the mortality for patients. Expected utilities and medical costs were based on the number of organ abnormalities. Health states were defined by the values of a set of attributes such as organ abnormalities, retinopathy, neuropathy, amputation, impaired physical appearance, hyperphagia, and female reproductive dysfunction. Metreleptin discontinuation was based on patient data or was assumed to be 2.05% per year when patient data were not available.

All patients in the NIH follow-up study were treated with metreleptin until death. A time-varying Cox proportional hazards model was used to estimate the relation between organ abnormality and mortality. Different parametric curves were fitted to the survival data from the trial, where the exponential curve showed the best fit.

Health utility estimates were derived from a discrete choice experiment (DCE) within the general population. These estimates were used to estimate QALYs associated with lipodystrophy.

Metreleptin is available in 11.3 mg vials (10 mg dose). However, the availability of smaller vial sizes (5.8 mg and 3 mg) is expected within the next three months. Given the anticipated availability of smaller vials, an average price per patient for metreleptin was assumed in the base case analysis. Resource use was based on questionnaires completed by two clinical advisers who treat lipodystrophy at Addenbrooke's Hospital. Health-state costs were based on

NHS reference costs. Only the cost of hypoglycaemic events was included in the model as adverse event.

Several assumptions were assessed in the sensitivity analysis, i.e., a price fall of 90% of metreleptin after 10 years, reduced initial price, elimination of mortality benefit of metreleptin for PL patients, changes to assumptions regarding organ abnormality progression, alternate survival extrapolation methods, and earlier treatment initiation. A deterministic one-way sensitivity analysis was conducted for the key clinical and economic variables in the model. A probabilistic sensitivity analysis (PSA) was also conducted.

When only 11.3 mg vials were included in the cost effectiveness analysis, the incremental cost effectiveness ratio (ICER) was £1,316,932 for metreleptin compared to SoC. The ICER was £671,927 per QALY gained for metreleptin compared to SoC when multiple vial sizes of metreleptin are available. When a PAS was applied to the scenarios of only 11.3 mg vials available and multiple vial sizes available, ICER yielded [redacted] and [redacted] per QALY gained respectively for metreleptin versus SoC. These values are higher than the thresholds used by NICE in HST appraisals.

1.7 Summary of the ERG's critique of the value for money evidence submitted

The ERG identified several critical issues with the company's economic analysis. Some of these issues were partially addressed in the revised electronic model submitted by the company in its response to the clarification letter. One of the most important concerns related to the organ impairment progression and matching methodology, which contributed directly or indirectly to a potential bias in favour of metreleptin treatment compared to SoC. The ERG requested that the company conduct *de novo* statistical analyses, in order to try to resolve these concerns. However, the company stated that they could not finalise this request given the timelines. There were also serious concerns surrounding the survival analyses conducted by the company and the implementation of these analyses in the model. There were several additional issues with the extrapolation of other attributes not related to organ damage and metreleptin discontinuation, which create potential bias in favour of metreleptin.

Overall, the ERG has serious concerns about the validity and reliability of the disutility weights reported by the company, and therefore considers these disutility weights to be speculative. The key concern is that the use of DCE to directly obtain disutility values for heath states is still in its infancy. The most striking issue relates to the fact that DCE classifies health states far more often below zero than TTO (time-trade-off) and produces lower average health state values. In addition, various major flaws in the design of the DCE and the analysis of the data were identified, leading to a negative assessment of the way QALYs are currently estimated.

The ERG also had several concerns about the resource use and costs included in the model. Furthermore, the ERG considered the validation of the model to be insufficient.

Given the many critical issues described above, it proved impossible for the ERG to give any indication on the cost-effectiveness of metreleptin. The uncertainty around the ICERs

presented by the company far exceeds that created by parameter uncertainty and reported in the CS.

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

The CS includes a budget impact model to estimate the total costs to the NHS for a period of five years of adopting metreleptin for LD patients in the UK. The results presented by the company suggest that the net budget impact of implementing metreleptin will be £18,762,893 in year 1, and will rise to £34,114,350 in five years. The cumulative net budget impact over the first five years will be £133,045,965. Additionally, the estimated total number of LD patient eligible for metreleptin treatment after five years is 44 and the uptake of metreleptin rises from 85% in year 1 to 90% in year 5.

The CS also includes estimates of the impact of metreleptin on (i) inability to work or attend school for patients and carers; (ii) estimates of out-of-pocket costs for patients and carers including costs related to diabetes, transportation, fertility and cosmetic treatment; and (iii) other carer costs.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health-related benefits

In general, the assumptions made in the budget impact analysis could be considered as plausible. However, there are some concerns about the expected uptake rate of metreleptin. The ERG considers the high expected uptake rate as reliable, but the reason behind the rising uptake rate from 85% in year 1 to 90% in year 5 is unclear since the company did not provide further details on these assumptions. Furthermore, the validity of the estimated discontinuation rate provided by the company remains unclear since detailed information on these assumptions were also not provided.

The ERG has some concerns related to the impact of metreleptin beyond direct health benefits. No costs associated with inability to work or attending school were calculated in the analyses. However, as part of the NIH follow-up study, data on these attributes were collected. The ERG notes that, while there were data collected on these attributes, the company did not find it possible to estimate associated costs; the reason for this is unclear. The ERG also questions the assertion in which the company stated that metreleptin will mitigate the costs of hospitalisation and fertility and cosmetic treatments, since no evidence was provided to support this assertion. No indirect health care costs, due to additional life-years after receiving metreleptin, were reported in the CS and the company stated that they expected that these costs would not influence the cost effectiveness results. In the opinion of the ERG, these costs should be included in the model for completeness. Finally, the CS does not include costs related to informal care and productivity loss for the caregiver. The company states that it is currently conducting research to gain more details of these issues, but the ERG considers it to be inadequate that the impact of lipodystrophy on informal carers was not identified prior to the CS.

1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty

Strengths: The ERG believes that the following represent strengths within the CS:

- The company's submission provided sufficient details for the ERG to appraise the searches, which were on the whole clear, transparent and reproducible. An adequate range of resources were searched.
- Despite the rarity of LD syndromes, the company has presented data from a large, multinational study of metreleptin treated patients.
- The ERG considers that the budget impact model is generally based on plausible assumptions.

Weaknesses: The following are the main weaknesses of the CS, observed by the ERG:

- The CS lacks information about the long-term effects of metreleptin treatment.
- The CS (section 9.9.2, page 121) states that: 'Over 85% of the 107 patients in study NIH 991265/20010769 received >1 year of metreleptin, 72% received >2 years, 54% received >3 years, and 28% received 6 or more years of metreleptin in this study. The maximum duration of therapy was 14 years.' Despite this, the reporting of long-term clinical effectiveness outcomes, in the CS, was limited to information on the persistence (up to 36 months) of changes in HbA_{1c} and triglycerides on metreleptin treatment.
- Where long-term outcomes were available (in the NIH follow-up study, not included in the CS), these were either inferred from changes in surrogate outcome measures (e.g. hepatic enzymes, 24-hour protein excretion, blood pressure), or lacked any definition (e.g. hyperphagia recorded in notes).
- The CS lacks information about UK lipodystrophy patients; only one patient in the metreleptin treatment studies and one patient in the natural history study used in the cost effectiveness analysis, were UK patients.
- Despite the existence of an early access programme (EAP), which includes UK patients and has been running for more than 10 years, no results from the EAP were included in the CS and no justification/explanation for this was provided.
- The study details and results for the NIH follow-up study and the GL/PL natural history study, which were used to inform cost effectiveness modelling, were not included in the clinical effectiveness section of the CS.
- Participants in the NIH follow-up study and the GL/PL natural history study were not comparable and it is not clear that the matching exercise reported in the CS was adequate to account for the apparent differences.
- The clinical effectiveness section of the CS does not include any assessment of the comparative effectiveness of metreleptin vs. standard care (either direct or indirect).
- The process used to identify and select comparator/natural history studies remains unclear; the company's response to clarification questions stated that: 'The clinical SLR was carried out to search for trials of both metreleptin and trials of relevant comparators (see Section 9.1 of the submission).' However, the searches reported in the relevant sections of the CS were specific to metreleptin/leptin replacement interventions and did

not include any terms to search for comparator studies; these searches would not have reliably retrieved studies of comparator interventions or natural history studies.

- There are several concerns related to the estimation of organ impairment progression. Due to these issues, the ERG has substantial concerns about the appropriateness of the statistical methods used by the company. Therefore, the ERG requested that the company conduct de novo statistical analyses, however, the company stated that they were not able to finalise this request due to the given timelines.
- Serious concerns regarding the survival analyses conducted by the company and the implementation of these analyses in the model were identified.
- There were also several issues related to the matching methodology conducted by the company.
- The ERG considers the derivation of the utility decrement from the company's DCE as invalid.
- The ERG considers the validation of the model to be inadequate.

Areas of uncertainty: There is considerable uncertainty about the long-term effects of metreleptin treatment, particularly in relation to patient-perceived symptoms and clinical outcomes. The clinical effectiveness section of the CS includes only very limited evidence about patient perceived symptoms (hyperphagia) and clinical outcomes (liver damage) and data are limited to one year. The 'post-metreleptin improvements' reported in the follow-up study, but not in the CS, are frequently based on measures taken at one year and use definitions based on changes in surrogate outcome measures (e.g. improvement in liver abnormality is defined as 20% reduction in alanine transaminase/aspartate transaminase ratio (ALT/AST) at year one in a patient who had elevated ALT/AST at baseline) or provide no definition at all. The follow-up study also included some information on newly emergent (on metreleptin treatment) lipodystrophy characteristics in patients with no evidence of these characteristics prior to metreleptin initiation. However, no indication of the timeframe of observation was provided. Broadly, these data indicate that new incidences of organ abnormalities (liver, kidney and heart) and female reproductive dysfunction continue to occur, in all categories of LD patient, on metreleptin treatment. However, the data presented are insufficient to allow an adequate assessment of how the rate of development of new abnormalities on metreleptin treatment would compare with that seen in patients on standard care.

There remains some uncertainty regarding the long-term effects of metreleptin on metabolic measures. The CS includes some information on the persistence (up to 36 months) of changes in HbA_{1c} and triglycerides on metreleptin treatment, however, these data indicate that the apparent effect of metreleptin on triglyceride levels may not be applicable to the overall PL population. The potential effects of neutralising antibodies on the long-term efficacy of metreleptin treatment remain unclear. In clinical trials (studies NIH 991265/20010769 and FHA101) included in the CS, most patients (95%) developed antibodies to metreleptin. Overall, in patients where antibody data were available, neutralising anti-drug antibody activity was observed in 38/102 patients (37%) and, of these 38 patients, 58% achieved resolution of neutralising antibodies; these data were not linked to information about long-term efficacy or any withdrawals from treatment due to lack of efficacy.

The observed effects of metreleptin are all based on changes from baseline in single arm metreleptin treatment studies. The lack of comparative studies means that the extent to which any observed effects may be attributed to metreleptin remains unclear.

The significance of pancreatitis, as an adverse event following withdrawal from treatment, remains unclear. The CS describes six incidences of pancreatitis as an adverse event, across the 148 lipodystrophy patients in the two included studies. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridemia. With reported non-compliance rates of between 9% and 19% the extent of the pancreatitis risk, for these patients, remains unclear and would appear to warrant further consideration.

There is no mention in the CS of possible stopping rules for metreleptin. Given the many differences between and within groups of patients with different lipodystrophy syndromes, it cannot be expected that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

Currently, only 11.3 mg vials of metreleptin are available. However, the company expects the availability of smaller vial sizes (i.e., 5.8 mg and 3.0 mg) within three months after submission.

1.11 Summary of exploratory sensitivity analyses undertaken by the ERG

The ERG identified some programming errors and corrected these programming errors to obtain a corrected version of the CS model. Even though these errors had a significant impact in total QALYs, the incremental results and ICER did not change significantly due to these corrections.

Given the many critical issues described earlier (Section 1.7), it proved impossible for the ERG to give any indication on the cost-effectiveness of metreleptin, thus no ERG base case was estimated. Based on the corrected company base case, the ERG conducted additional exploratory scenario analyses, challenging some of the structural assumptions of the model as well as some key input parameter choices.

It appears that the cost effectiveness results are very much dependent on the dosage assumptions of metreleptin (multiple vial size or single vial size), the treatment effect of metreleptin on disease attributes and utility input choice.

The ERG does not consider the cost-effectiveness model as reliable and trustworthy enough to inform decision making on the cost-effectiveness of metreleptin. The uncertainty around the company-reported ICERs is much larger than suggested by the PSA, which only addresses parameter uncertainty. However, the ERG still expects decision uncertainty to be rather low, as the ICER values, even in the best cases that the company presented, are significantly above the accepted thresholds.

2. BACKGROUND

2.1 Introduction

This chapter presents an overview of Lipodystrophy (LD) and its management. The content of this chapter is based on relevant literature, information provided by clinical advisors to the Evidence Review Group (ERG) and information presented in the background sections of the company's submission (CS).[1] For additional information on the aetiology, epidemiology, health impact, prognosis and management of LD, please see the CS (pages 32 to 61).

2.2 Description of health problem

2.2.1 Disease overview

The term lipodystrophy describes a heterogeneous group of rare disorders, which are characterised by a deficiency of adipose tissue (body fat) without underlying nutritional deprivation.[1, 2] Lipodystrophy syndromes are associated metabolic abnormalities, including diabetes mellitus (DM), hypertriglyceridemia and steatohepatitis,[1, 2] and with organ damage consequent upon ectopic lipid storage.[2]

Lipodystrophy syndromes are categorised by aetiology (genetic or acquired) and by the distribution of adipose tissue deficiency (generalised, affecting the entire body, or partial). This results in four major categories: congenital generalised LD (CGL), acquired generalised LD (AGL), familial partial LD (FPL) and acquired partial LD (APL).[1, 2]

Congenital Generalised Lipodystrophy

Congenital generalised lipodystrophy, also known as Berardinelli-Seip syndrome, is an autosomal recessive disorder with multiple genetic causes, which is characterised by an almost complete lack of body fat and prominent muscularity staring at birth or in infancy.[1-4] Soon after birth, patients with CGL exhibit insatiable hunger and accelerated linear growth rates. [1-3] Infants may develop hepatosplenomegaly and umbilical prominence or hernia.[3] Additionally, patients may have phlebomegaly and acanthosis nigricans later in childhood.[2, 3] A few patients develop DM during infancy, but development of DM most frequently occurs during the teenage years or later.[3] Diabetes, hypertriglyceridemia and hepatic steatosis can lead to the development of diabetic complications (nephropathy, neuropathy and retinopathy), recurrent attacks of acute pancreatitis, cirrhosis of the liver, and heart disease (cardiomyopathy, heart failure, myocardial infarction, arrhythmia), which are major causes of morbidity and mortality.[2, 3]

Acquired Generalised Lipodystrophy

Acquired generalised lipodystrophy, also known as Lawrence syndrome, is more common in females (female:male ratio 3:1) and appears usually before adolescence (but may develop at any time in life) with progressive loss of fat affecting the whole body including palms and soles of the feet.[1, 2, 5] The pattern and extent of fat loss in AGL is variable; most patients have generalised fat loss, but in a few cases some areas of the body (e.g. intra-abdominal and bone marrow fat) are spared.[3] As with CGL, AGL patients are highly likely to develop DM, hypertriglyceridemia and hepatic steatosis.[3, 4] Approximately 25% of AGL cases are associated with panniculitis (which presents clinically as subcutaneous inflammatory nodules), 25% with

autoimmune disease, and 50% are of idiopathic origin.[1, 3, 6] Autoimmune disorders that have been associated with AGL include juvenile-onset dermatomyositis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome.[1, 3, 7]

Familial Partial Lipodystrophy

Familial partial lipodystrophy is a group of usually autosomal dominant disorders, characterised by loss of fat affecting the limbs, buttocks and hips.[2, 3] The various forms of FPL are extremely rare.[1, 4] Numerous genetic mutations have been identified for FPL including the LMNA gene in familial PL type 2 (FPLD2).[1, 8]The most prevalent form of FPL is FPLD2, also known as the Dunnigan-Variety.[1, 4] FPLD2 develops during puberty, resulting in gradual atrophy of subcutaneous fat in the extremities followed by fat loss in the anterior abdomen and chest, giving the appearance of increased muscularity.[1, 4] Patients also have fat accumulation in the face, neck, and intraabdominal areas, causing a Cushingoid appearance.[1, 2, 9]Metabolic complications are common in adulthood,[10] with associated increased risk of heart disease.[11]

Acquired Partial Lipodystrophy

Acquired partial lipodystrophy, also known as Barraquer-Simons syndrome, usually has a childhood or adolescent onset and is more common in females (female:male ratio 4-5:1).[1, 2]APL is distinguishable from other LD syndromes by the unique cephalocaudal progression of subcutaneous fat loss that is observed.[1, 2, 4] Subcutaneous adipose tissue loss begins in the face and subsequently spreads to the neck, upper extremities, thorax and abdomen.[1, 2, 4] The lower extremities, lower abdomen and gluteal region do not exhibit lipoatrophy but rather accumulate excess adipose tissue.[1, 2, 4, 12] With the exception of hepatomegaly, metabolic complications are rarely seen in association with APL.[1, 12] APL is associated with autoimmune disease, particularly membranoproliferative glomerulonephritis (MPGN), in approximately 20% of cases.[2, 12]

2.2.2 Epidemiology

The CS states that there are limited published data available on the incidence and prevalence of LD in England. One recent study is cited, Chiquette et al. 2017,[13] however, the CS states that this study 'was not deemed accurate or generalisable for a UK population and the anticipated metreleptin licence.' Chiquette et al. used two approaches, one based on identification of cases from five electronic medical record (EMR) databases including the United Kingdom General Practice Research Database (GPRD), and one based on searches of the published literature, to estimate the prevalence of all LD.[13] The estimated worldwide prevalence of all LD, based on EMR database searches of four USA databases and the UK GPRD, was 3.07 cases/million (95% CI: 2.30 to 4.02).[13] No separate estimate was reported for the UK. The estimated European Union (EU) prevalence estimate, based on the total number of LD cases identified from searches of the published literature adjusted for underreporting and extrapolated to the total EU population, was 2.63 cases/million.[13] The study authors state that their estimates are at the lower end of the range of previously published numbers and that their approach may have underestimated prevalence.

The CS (CS, section 6.2, page 42-43) states that: 'More relevant and accurate estimates are available based on early access programme (EAP) data from a decade of metreleptin use in UK

clinical practice at Addenbrooke's. There are currently [redacted] LD patients receiving metreleptin at Addenbrooke's under the EAP – [redacted]. Of these patients, some may have initiated metreleptin over a decade ago since the beginning of the EAP. As the EAP has been running for over 10 years it is expected that the number of patients on the programme is a good indicator of the number of eligible patients in England. Clinicians from Addenbrooke's Hospital in England who are involved in the UK EAP have been consulted to provide an estimate of the number of new GL and PL patients each year who would be eligible for metreleptin. Based on expert clinical opinion, it is assumed that [redacted] new patients each year would be eligible for metreleptin treatment ([redacted]).' The estimates in table D58 (CS, page 199) give an indication of the expected number of UK patients who will be eligible for metreleptin treatment over the next five years, increasing from 26 in year 1 to 44 in year 5; these estimates were based on Addenbrooke's EAP data and expert opinion.

ERG comment: The CS estimates of the numbers of UK patients eligible for metreleptin treatment appear low when compared to published estimates of the prevalence of LD; the number of patients currently treated divided by the estimated total population for England and Wales 26/58.38 million gives an estimated prevalence of approximately 0.45 cases/million. The reason for this discrepancy is unclear. Given that only some of the patients in England and Wales, who have LD, are currently eligible for treatment with metreleptin under the UK EAP at Addenbrooke's Hospital:

'Recombinant leptin is specifically indicated for patients with severe LD and low leptin levels (<10 μg/L). The national service will select and treat patients with leptin as is clinically indicated. The cost of leptin is expressly excluded from the funding for this service.'[1]

It is possible that approval by NICE based on the licenced indication may result in a higher proportion of patients with LD being eligible/considered for metreleptin treatment. This is a particular concern if the licensed indication follows the outline suggested in the latest available information (09/03/2018) i.e [redacted] Whilst the EAP at Addenbrooke's Hospital and associated criteria for treatment are well established (>10 years duration), the ERG notes that there is uncertainty around the issue of future patient numbers.

2.2.3 Aetiology

Lipodystrophy syndromes can be inherited or acquired. Autosomal recessive CGL and autosomal dominant FPL are the two most common types of genetic LD. Mutations in the *AGPAT2*, *BSCL2*, *CAV1* and *PTRF* have been reported in patients with CGL, and mutations in *LMNA*, *PPARG*, *AKT2* and *PLIN1* have been reported in patients with FPL.[3] Acquired LD can be caused by autoimmune disease, drug or vaccine injections, and panniculitis; around 50% of acquired LD is of unknown origin.[3] An important sub-type of acquired LD occurs with prolonged exposure to protease-inhibitor-containing antiretroviral therapy in HIV-infected patients.[3]

ERG comment: The CS reports the exclusion of specific aetiologies of acquired LD (table C11, page 69 of the CS):

- HIV-associated LD
- LD secondary to drug administration (insulin growth hormone, steroids, antibiotics and vaccinations)
- LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections

The scope issued by NICE does not exclude these sub-types of LD. Furthermore, the search strategies reported in the CS, for both clinical evidence (Appendix 1, page 220-223 of the CS) and economic evidence (Appendix 3, page 225-227 of the CS) included terms for HIV-associated LD.

2.2.4 Pathogenesis

Subcutaneous adipose tissue loss is a primary feature of LD, regardless of the sub-type and hence levels of the adipocyte-secreted hormone leptin are very low in these patients.[1, 14] Leptin promotes satiety (the feeling of feeling full), leading to decreased food intake,[1, 15] and also decreases gluconeogenesis in the liver and adipose tissue and increases glucose utilisation in skeletal muscle by activating signalling pathways which overlap with, but are not identical to, those of insulin.[1, 16] Leptin may also protect peripheral tissues from lipotoxicity by stimulating fatty acid oxidation.[1, 17] A deficiency in leptin can therefore result in insatiable hunger, increased gluconeogenesis and reduced fatty acid oxidation.[1] People with LD syndromes often have severe hypertriglyceridemia, with serum levels in the range of 1,000 mg/dL [11.29 mmol/L] compared with normal levels of 150 mg/dL [1.69 mmol/L]) being reported.[1, 18] The accumulation of ectopic fat throughout the body is associated with severe insulin resistance, resulting in the development of hyperglycaemia and HbA_{1c} levels consistent with a diagnosis of DM.[19, 20] These metabolic complications are drivers of the morbidity and mortality associated with LD syndromes.[2, 5]

2.2.5 Clinical features

Micro- and Macro-vascular complications

Elevated triglyceride levels have been found to be independently predictive of myocardial infarction, ischaemic heart disease and death, in large general population studies.[21] Two small studies have reported increased prevalence cardiovascular disease in patients with FPL, compared to unaffected family controls. One study reported atherosclerotic vascular disease in 12/39 (31%) of FPL patients compared to 6/45 (13%) of unaffected controls, however, it should be noted that rates of cigarette smoking were also higher in the FPL group, 13/39 (33%), than in unaffected controls, 9/45 (20%).[22] A second study, compared metabolic and clinical outcomes in *LMNA* mutation carriers with FPL and insulin resistance to matched family controls;[11] 8/23 (35%) of FLP patients had coronary heart disease (CHD), compared to 1/17 (6%) of controls, and all FLP patients had developed CHD before the age of 55 years.[11]

With respect to cardiomyopathy, a study of 44 GL patients reported that they found echocardiographic evidence of LV hypertrophy, as well as ECG abnormalities in 'more than half of patients,' with rates varying by type of GL.[23] This study also reported that, 'Although

cardiomyopathy was a frequent finding in our lipodystrophy patients, we found severe heart failure in only 2 patients.'[23] Review articles have reported that heart disease (cardiomyopathy, heart failure, myocardial infarction and arrhythmia) is a major cause of mortality in people with LD.[2, 3]

ERG comment: The CS tends to overstate the evidence about hypertriglyceridemia and heart disease in LD. For example, section 6.1.3.1, pages 37-38 of the CS, states: 'In the Copenhagen City Heart Study, which was initiated in 1976 and has followed 19,329 subjects, each 1 mmol/L increase in triglycerides is associated with a 40% increase in risk for myocardial infarction (MI), a 25% increase in risk for ischemic heart disease, and an 18% increase in risk of death in women, and 16%, 12%, and 10% increased risks, respectively, in men, when adjusted for age and HDL-C.'[1] These numbers are not reported in the cited study and are not consistent with the multifactorially adjusted hazard ratios (HRs) which are reported: For women these were 1.20 (95% CI: 1.05 to 1.37) for MI, 1.10 (95% CI: 0.99 to 1.21) for ischaemic heart disease and 1.18 (95% CI: 1.10 to 1.27) for total death; for men the corresponding values were 1.04 (95% CI: 0.98 to 1.11) for MI, 1.00 (95% CI: 0.95 to 1.06) for ischaemic heart disease and 1.08 (95% CI: 1.03 to 1.13).[21] It is also important to note that estimates of the risks associated with elevated triglyceride levels, which are derived from general population studies, should not be assumed to be directly transferable to patients with LD syndromes.

Renal failure and pancreatitis

Review articles have reported that patients with LD syndromes and hypertriglyceridemia and severe insulin resistance are pre-disposed to developing acute pancreatitis, cirrhosis, ESRD requiring renal transplantation and blindness due to diabetic retinopathy.[1-3] Chronic renal disease and membranoproliferative glomerulonephritis (MPGN) can occur in patients with GL and PL due to longstanding, suboptimally controlled DM.[1] Approximately one-fifth of patients with APL will develop MPGN, which can be fatal in some patients.[1, 3, 12] The CS (section 6.1.3.2 of the CS, page 38) states that, in the pivotal study NIH 991265/20010769, 31% of patients reported a history of pancreatitis (33 of 107).[1]

ERG comment: The CS (section 6.1.3.2, page 38) also includes the following statement: 'Additionally, one of the primary concerns with hypertriglyceridemia, especially when triglyceride levels exceed 1,000 mg/dL (11.29 mmol/L), is the risk for acute pancreatitis which can be life-threatening with a high mortality rate of 40% to over 50% when accompanied by complications like infection or organ failure.'[1] However, no reference is provided to support this statement.

Liver disease

Ectopic fat distribution in LD can lead to reduced liver function, and the development of cirrhosis and non-alcoholic fatty liver disease (NAFLD).[1, 2, 24] Liver failure, gastrointestinal haemorrhage, hepatocellular carcinoma have also been identified as causes of mortality amongst patients with LD.[2] An open-label, prospective study of metreleptin therapy in 27 patients with inherited and acquired forms of LD reported a reduction in mean NAFLD activity score, from 4.3 at baseline to 2.4 on treatment; patients who had fibrosis at baseline remained stable on treatment.[24]

A review of 63 cases of AGL from the literature and report of an additional 16 cases found hepatomegaly in approximately 72% of patients.[6] In this review, 50% of patients with AGL had elevated alanine aminotransferase (ALT) levels.[6]

ERG comment: The CS (section 6.1.3.3, page 38) incorrectly reports the results from the review of AGL patients, described above, as 84% with hepatomegaly and 60% with elevated ALT; a different study, by the same authors is erroneously cited.[12]

The CS (section 6.1.3.3, page 38) also states that: 'Non-alcoholic steatohepatitis (NASH) is highly prevalent in patients with LD, and there are no treatment options current available to treat this condition.' A study which makes no mention of NASH[9] is cited in support of this statement.

Hyperphagia

Low leptin levels act on the brain as a starvation signal, and therefore patients with LD can experience insatiable hunger and hyperphagia.[1, 25] As described above (section 2.2.4), hyperphagia due to leptin deficiency is also a key driver of morbidity associated with LD syndromes.[1] Patients with LD cannot store excess calories in their adipose tissue, and instead they are deposited as ectopic fat in the liver and muscle, causing severe insulin resistance, diabetes mellitus, hypertriglyceridemia, and steatohepatitis.[1, 4, 9]

Hyperphagia can also affect the management of LD. Dietary modifications are required to manage the metabolic complications of LD, however, dietary restriction may be challenging to achieve in some patients due to hyperphagia.[2, 25, 26] In addition, in children food restriction must be balanced by requirements for growth.[1, 2]

Fatigue and pain

Patients with LD syndromes may experience fatigue and pain due as part of their disease course. In a review of 16 case reports of patients with AGL treated at a single treatment centre in the US, patients presented with pain at diverse sites. While no quantitative data were gathered, pain was reported in knee joints, abdomen, calf muscle and skin by one patient each.[6] The case descriptions suggested that pain could be attributed to a number of different underlying causes. For example, one patient presented with pain in the calf muscle, which was suggestive of intermittent claudication.[6] Another patient developed painful skin lesions over her legs and thighs alongside abdominal pain.[6] An additional patient had pain in both knee joints, while loss of plantar fat in the feet was associated with the development of "painful" callosities, which limit movement.[6] In addition, one patient reported general fatigue.[6]

ERG comment: The scope issued by NICE[27] does not include pain in the list of specified outcomes and the clinical effectiveness section of the CS (CS, pages 67 to 123) does not include any evidence about effects of metreleptin treatment on pain.

Physical appearance

The partial and generalised loss of subcutaneous fat as well as abnormal fat distribution can have a marked effect on the physical appearance of patients with GL and PL. In CGL, patients may have prominent muscles, phlebomegaly, acanthosis nigricans, and umbilical prominence.[1,

[2] In AGL, patients may also have severe adipose tissue loss from the palms, soles, and intraabdominal area.[1, 4] The loss of subcutaneous adipose tissue in FPL can affect the appearance of the limbs, buttocks and hips. Additionally, excess fat accumulation, which varies by FPL subtype, may result in a Cushingoid appearance (including facial roundness).[1, 2] The distinguishing physical features of APL include cephalocaudal progression of fat loss, beginning in the face and subsequently spreading to the neck, upper extremities, thorax and abdomen.[1, 2] The CS includes anonymised patient photographs illustrating the morphology of generalised (Figure B3, page 40 of the CS) and acquired (Figure B4, page 41 of the CS) LD syndromes.[1]

Depression and neurological affects

The CS (section 6.1.3.7, pages 41-42) states that the disease course of LD may have negative consequences for patients' psychological health, and that physical dysmorphia, insatiable hunger and hyperphagia, infertility, fatigue and pain may contribute to depression in patients.[1] A 2016 practice guideline on the diagnosis and management of LD syndromes states that: 'Patients should be assessed for distress related to lipodystrophy and referred as necessary to mental health professionals and/or plastic surgeons.'[2]

Additionally, neurological deficits may also occur in GL and PL.[1] A 2017 systematic review reported rates of intellectual disability of 50% in patients with AGL, 47% in patients with CGL, 43% in patients with FPL and 8% in patients with APL, respectively.[5]

ERG comment: The CS (section 6.1.3.7, pages 41-42) also includes the statement: 'In a survey of LD experts in Europe, depression was considered to be of clinical importance and, anecdotally, occurs at a medium-high frequency amongst patients with GL and PL.' [1] An article about fertility and obstetric complications in women with FPL, which makes no mention of depression or anxiety, was erroneously cited in support of this statement.[1]

The scope issued by NICE[27] does not include depression or anxiety in the list of specified outcomes and the clinical effectiveness section of the CS (CS, pages 67 to 123) does not include any evidence about effects of metreleptin treatment on depression and anxiety.

Infertility and PCOS

Hypogonadotropic hypogonadism leading to delayed puberty, infertility, and abnormalities in the menstrual cycle, hirsutism and polycystic ovary syndrome (PCOS) in women, have are common in patients with LD syndromes.[2, 10, 28, 29]

A study comparing fertility and obstetric complications in women who had FPL due to LMNA to the general population and unaffected familial controls, found that 54% of the women with LMNA mutations exhibited clinical PCOS phenotypes, 27% had infertility, 50% experienced at least one miscarriage, 36% developed gestational diabetes and 14% experienced eclampsia and foetal death.[10] In the general population, 4.8% of women have PCOS, 10% have infertility, 10.1% experience at least one miscarriage, 5–10% have gestational diabetes and 2.6% experience eclampsia and foetal death.[10]

2.2.6 Diagnosis

Firm diagnostic criteria have not been established for LD.[2] The American Association of Clinical Endocrinologists (AACE) and a 17 member committee of nominees from worldwide endocrine societies have both attempted to develop consensus recommendations for the detection and diagnosis of LD.[2, 30]

The differential diagnosis should include conditions presenting with severe weight loss (malnutrition, anorexia nervosa, uncontrolled DM, thyrotoxicosis, adrenocortical insufficiency, cancer cachexia, HIV-associated wasting, chronic infections).[2] Differentiating between LD syndromes and uncontrolled DM is particularly difficult as both may present with extreme hypertriglyceridemia, however, restoration of glycaemic control in non-LD DM leads to restoration of body fat.[2] Generalised LDs can be confused with mutations of the insulin receptor or acromegaly, and FPL can be confused with Cushing's syndrome, truncal obesity and multiple symmetric lipomatosis.[2]

The multi-society practice guideline on the diagnosis and management of LD syndromes, which was published in 2016,[2] recommends that diagnosis be initially be based on history, physical examination, body composition and metabolic status, and further states that confirmatory genetic testing is helpful in suspected familial LD and should also be considered in at-risk family members.[2] The guideline also states that serum complement levels and autoantibodies may support the diagnosis of acquired lipodystrophy syndromes, and that there is no defined serum leptin level that can be used to establish a diagnosis of LD.[2] In patients with LD, the guideline recommends screening for comorbidities associated with the disease including diabetes, dyslipidaemia, NAFLD and cardiovascular and reproductive dysfunction.[2]

Differentiation of genetic and acquired LD can be hampered by the heterogeneity of subcutaneous adipose tissue loss between LD types. With CGL, patients typically have a lack of subcutaneous adipose tissue from infancy, whereas adipose tissue may appear as normal in infancy in patients with AGL.[2] The presence of autoimmune disease increases the suspicion of an acquired subtype.[1, 2]

AACE have conducted a MEDLINE literature search and panel discussion to inform their consensus statement on the detection of LD.[30] Although it does not have the structure of a guideline, the content of this statement is consistent with the practice guideline described above.

2.2.7 Prognosis

A recently published systematic review of the clinical features and management of non-HIV-related LD in children included 351 studies (including 219 case reports) of 1,141 patients; adult patients identified were excluded if the onset of LD had occurred after 18 years of age.[5] The review included 519 patients with CGL, 86 patients with AGL, 124 patients with FPL and 124 patients with APL.[5] The geographic distribution of the studies included in this review is not clear, however, the review does report some mortality data.

Of the 502 patients with CGL whose mortality status was known at the time of being reported (mean age at reporting, 12.6 years), 33 were dead; the mean age at death was 12.5 years (range, 0.4 to 46.0 years), with respiratory infection the most frequently reported cause of death, followed by cardiac failure.[5] Donohue syndrome resulted in a high mortality rate of 50% (21 of 42 patients dead at reporting) and a relatively early mean age at death (1.2 years; range, 0.03 to 8.3 years), with respiratory infection the most common cause.[5] Nine AGL patients were dead at the time of reporting and the mean age at death for these patients was 32.2 years, range 4.0 to 82.0 years.[5] For partial lipodystrophy, seven FPL patients were dead at the time of reporting and the mean age at death was 27.8 years (range 1.0 to 77.0 years), and three APL patients were dead at the time of reporting, with the mean age at death being 22.7 years (range 12.0 to 44.0 years).[5]

ERG comment: The CS (section 6.3, page 43) states that there are no natural history studies of LD patients in England (or the UK) to inform on the life expectancy of people with the disease in England. However, the CS does not present any search strategies used to identify natural history studies. In addition, no information was provided about survival/age at death for patients diagnosed during adulthood; it is likely that considering only patients diagnosed during childhood (as above) will result in lower estimates for mean age at death.

2.2.8 Impact on patients' health-related quality of life (HRQoL)

The CS (section 7.1, page 44) states that there is a paucity of published studies evaluating health-related quality of life (HRQoL) in patients with LD and their families. A literature review conducted to inform the CS (described in section 10.1.5, pages 132-135) identified one conference abstract reporting an evaluation of HRQoL in LD patients from the Lipodystrophy Connect Register, a global registry which collects self-reported data from both patients and care givers.[31] The study used a QoL questionnaire, which included items from the Patient Reported Outcomes Measurement System (PROMIS) short forms, questions on financial impact and impact of pain; 58/126 (48%) of participants responded to the QoL questionnaire.[31] Of the responders, 97% were female and 84% had partial LD.[31] EQ-5D scores were estimated from PROMIS global health items.[31] The estimated mean EQ-5D score for the LD syndromes population was 0.67, compared to a general population estimate of 0.866.[31] The abstract also noted that patients with LD syndromes reported some impairment in QoL on domains of physical health, mental health, social isolation and stigma, compared to the general population, however, no domain-specific data were presented.[31]

ERG comment: The CS also states that: 'Interviews with patients with LD conducted at the NIH in the US on behalf of Aegerion demonstrates the negative impact of LD.' (CS section 7.1, page 44). This statement is referenced as 'Aegerion Pharmaceuticals Ltd. Lipodystrophy patient research (NIH). Data on file. 2017.' These data were not provided; selected quotes from patients and carers are presented (CS: Figure B5, page 45; Figures B6 and B7, page 46; Figures B8 and B9, page 48).

2.3 Current service provision

The CS states that Aegerion are not aware of any NICE clinical guidelines, NICE pathways or published national guidelines on the management and treatment of LD. Metreleptin is the only

drug specifically for the treatment of LD. In the UK, treatment with metreleptin is currently provided, as part of an early access programme (EAP), under the National Severe Insulin Resistance Service at Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust. An overview of the NHS service specification (A03/S(HSS)/b)[32] is provided in the CS (CS, section 8.1.1, Table B9).

The CS states that: 'There is currently no standard clinical pathway for the treatment of LD in England.'[1] Standard care comprises an energy-restricted diet to lower triglycerides and glucose, which can be supplemented by treatments aimed at reducing complications such as DM (oral antidiabetic drugs including oral medications such as metformin, and injectable therapies including GLP-1 agonists in some patients and/or insulin) and hypertriglyceridemia (fibrates, statins).[1] Sections 8.1.2 and 8.2 of the CS (pages 58-61) provide a description of the various management options.

2.4 Description of the technology under assessment

Metreleptin is a leptin replacement therapy administered to address the effects of leptin deficiency in the population of LD patients with low leptin levels. It is a recombinant human leptin analogue produced in Escherichia coli cells by recombinant DNA technology to form recombinant methionyl-human leptin.[1, 33]

3. CRITIQUE OF THE COMPANY'S INTERPRETATION OF THE DECISION PROBLEM

3.1 Introduction

The remit of this appraisal, as defined in the final agreed NICE scope,[27] is to evaluate the benefits and costs of metreleptin within its licensed indication for treating lipodystrophy for national commissioning by NHS England. The final NICE scope outlines the agreed population, intervention, comparators and outcomes for the appraisal.[27] The NICE scope also sets out wider considerations relating to the impact of the technology beyond direct health benefits and on the delivery of the specialised service, the nature of the condition, costs to the NHS and PSS and value for money.

At the time of submission of the ERG report, metreleptin did not have a marketing authorisation in the UK for the treatment of lipodystrophy.

3.2 Adherence to the decision problem

Table 1 presents a summary of the decision problem as set out in the NICE scope[27] and the company's adherence to this (based on information presented on pages 19-23 of the CS).[1]

Table 1: Adherence to the agreed decision problem, as reported in the CS

	Final scope issued by NICE	Deviations of submission from the scope
Population	People with generalised or partial lipodystrophy	The original indication being sought from the European Medicines Agency (EMA) was as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency: • in patients with congenital or acquired GL, in adults and children 2 years of age and above • in patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA_{1c} ≥6.5%, in adults and children 2 years of age and above uncontrolled on standard therapy Clinical efficacy and safety data from the clinical trials included a subgroup of PL patients related to the original indication, in addition to all eligible PL and GL patients. Of note, the definition of the PL subgroup and the age thresholds is currently under discussion in the regulator process and is likely to change prior to approval. The following indication is based on Day 180 questions: • in patients with congenital or acquired GL, in adults and children 6 years of age and above; • in patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA_{1c} ≥8%, in adults and children 12 years of age despite optimized standard treatment
Intervention	Metreleptin	No deviations from scope
Comparator(s)	Established clinical management without metreleptin (including diet and lifestyle	No deviations from scope

	Final scope issued by NICE	Deviations of submission from the scope
	modifications, lipid lowering drugs and medications for diabetes)	
Outcomes	The outcome measures to be considered include: • Improvement in metabolic abnormalities • Liver function (including cirrhosis) • Glucose control and diabetes (including complications of diabetes and need for diabetes therapies) • Satiety • Pancreatitis • Use of other drugs • Organ damage including heart and kidneys • Growth and development • Reproductive dysfunction • Infection • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers; including effects on appearance)	The outcome measures considered in the cost effectiveness assessment base case include: • improvement in metabolic abnormalities (e.g. triglycerides) • liver function (including cirrhosis) • glucose control and diabetes • satiety / hyperphagia • pancreatitis • organ damage to liver, heart and kidneys • reproductive dysfunction • mortality (linked to level of organ abnormalities) • adverse effects of treatment • Ability to perform school or work • health-related quality of life (for patients and carers; including effects on appearance) Other outcomes considered but not included in cost effectiveness assessment base case • improvement in other metabolic abnormalities (e.g. beyond triglycerides) • use / discontinuation of other drugs (including diabetes therapies such as insulin) • organ damage beyond liver, heart and kidneys • growth and development • infections • direct mortality benefit of treatment (e.g. beyond impact on organ abnormalities)

	Final scope issued by NICE	Deviations of submission from the scope
		• anxiety/depression • chronic pain and muscle spasms • complications of diabetes including retinopathy, neuropathy, and amputation (e.g. toes, limb) • impact on family and caregivers including ability to perform work • adverse effects of treatment • female infertility Potential adverse effects of treatment such as hypoglycaemia, the development of neutralising antibodies, and lymphoma were considered and their impact on patient preferences was assessed. However, due to the lack of robust information on their prevalence and the incremental role of metreleptin on their occurrence, their impact was not included in the base case cost effectiveness analyses.
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	No deviations from scope
Impact of the new technology	• Overall magnitude of health benefits to patients and, when relevant, carers • Heterogeneity of health benefits within the population • Robustness of the current evidence and the contribution the guidance might make to strengthen it	No deviations from scope
Cost to the NHS and Personal Social Services (PSS), and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year	No deviations from scope

	Final scope issued by NICE	Deviations of submission from the scope
	• Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialist service • Staffing and infrastructure requirements, including training and planning for expertise	No deviations from scope
Other considerations	• If the evidence allows, subgroups according to whether the lipodystrophy is generalised or partial, or congenital or acquired, and according to the presence of complications associated with lipodystrophy (including diabetes and hypertriglyceridemia) will be considered • Guidance will only be issued in accordance with the marketing authorisation • Guidance will take into account any Managed Access Arrangements	Subgroups included in the model were identified based on the labelled indication. The following subgroups were included in the economic analysis: GL; PL; CGL; all NIH patients including those who do not meet the label indication
Related NICE recommendations and NICE Pathways	None	None

	Final scope issued by NICE	Deviations of submission from the scope
Related National Policy	NHS England. *Manual for Prescribed Specialised Services 2017/18. Chapter 62: highly specialist metabolic disorder services (adults and children), 2016 [Internet]*, 2017 [accessed 4.4.18]. 382p.[34] Available from: https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf Department of Health. *The national service framework for long-term conditions [Internet]*. Leeds, 2005 [accessed 4.4.18]. 106p.[35] Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/198114/National_Service_Framework_for_Long_Term_Conditions.pdf Department of Health. *NHS Outcomes Framework: at-a-glance [Internet]*, 2016 [accessed 4.4.18]. 5p.[36] Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/513157/NHSOF_at_a_glance.pdf	None

ERG comment: The latest available information (09/03/2018) is that: [redacted]

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The population included in the clinical effectiveness sections of the CS relates to people with generalised and partial lipodystrophies.

A subgroup of the partial lipodystrophy population is also described (patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L). The CS describes this subgroup as related to the original EMA licenced indication, which was for adults and children over two years of age with CGL or AGL, and adults and children over two years of age with FPL or APL characterised by leptin levels <12 ng/ml with triglycerides ≥5.65 mmol/L and/or HbA_{1c} ≥6.5%, uncontrolled on standard therapy.

The CS (Table A1, pages 19-20) describes a further population of interest, based on EMA day 180 questions: adults and children aged six years and over, with CGL or AGL; adults and children aged 12 years and over, with FPL or APL characterised by leptin levels <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA_{1c} ≥8%. The studies included in the clinical effectiveness section of the CS appear to have included GL patients <2 years of age and some patients in the PL subgroup with leptin levels >12 ng/ml, triglyceride levels <5.65mmol/ml and HbA_{1c} <6.5%. Five of the 66 GL patients included in the NIH 991265/20010769 were under six years of age and one was under two years of age, 40/66 (60.6%) of GL patients and 16/31 (51.6%) of PL subgroup patients had triglyceride levels <5.65 mmol/L, and 17/66 (25.8%) of GL patients and 2/31 (6.5%) of PL subgroup patients had HbA_{1c} <6.5%. None of the patients in the FH101 study were under six years of age, however, 6/9 (66.7%) of GL patients and 6/7 (85.7%) of PL patients had triglyceride levels <5.65 mmol/L, and 3/9 (33.3%) of GL patients and 1/7 (14.3%) of PL patients had HbA_{1c} <6.5%.[37, 38]

The clinical effectiveness section of the CS did not include any subgroup data for genetic and acquired LD syndromes.

ERG comment: The extent to which the population included in the clinical effectiveness sections of the CS is consistent with licenced indication for metreleptin remains unclear; at the time of submission of the ERG report, metreleptin does not yet have a UK licence for the treatment of LD syndromes. The latest available information (09/03/2018) suggests that: [redacted]

[redacted]

Of further note is the following information, provided in the company's response to clarification questions:[39] 'In NIH 991265/20010769 there was one patient from the UK (patient 901-026; 51 years, male, with AGL) who received metreleptin for 248 days (24/10/2003 to 27/06/2004). The patient was discontinued early because ineligibility was determined. Study FHA101 only included patients from the US. The NIH Follow-Up study also includes information for the same UK patient included in NIH 991265/20010769 (patient NIH-026). The Natural History study collected data for patients with lipodystrophy who were not treated with metreleptin at five locations: two in the US, one in Turkey, and two in Brazil (data collection in Brazil is ongoing). One patient from the UK, a female with APL diagnosed at age 42, was cared for at NIH and is included in the study.' This information raises concerns about the applicability, to the UK NHS, of information used in the CS.

3.3.2 Interventions

It is unclear whether the studies included in the CS describe metreleptin use in line with its licenced indication; at the time of submission of the ERG report, metreleptin does not yet have a UK licence for the treatment of LD syndromes.

In the CS (Table A2, pages 24-25), the recommended starting dose for metreleptin is reported as:

- Males and females ≤40 kg: 0.06 mg/kg
- (injection volume: 0.012 ml/kg)
- Males >40 kg: 2.5 mg (0.5 ml)
- Females >40 kg: 5 mg (1 ml)

With dose adjustments based on clinical response (e.g. inadequate metabolic control) or other consideration (e.g. tolerability issues, excessive weight loss especially in paediatric patients:

- Males and females ≤40 kg: maximum 0.13 mg/kg (0.026 ml/kg)
- Males >40 kg: maximum 10 mg (2 ml)
- Females >40 kg: maximum 10 mg (2 ml)

The recommended dosing frequency was once daily.

Participants in the studies included in the clinical effectiveness section of CS were treated with metreleptin, with the recommended dose ranges, given once daily or BID.

3.3.3 Comparators

The CS (section 12.1.2, page 153) states that the comparator for the cost effectiveness analysis was standard clinical management without metreleptin (including lifestyle modifications such as diet and exercise, use of lipid lowering drugs; and medications for diabetes). However, no data for the comparator were included in the clinical effectiveness section of the CS.

ERG comment: There are serious problems with the identification, selection and reporting of comparator data in the CS. No systematic attempts to identify comparator studies and no selection criteria for such studies are reported. Parameters for the standard of care arm, in the cost effectiveness analysis, were informed by a single natural history study, which was not included in the CS.

The company's response to clarification questions[39] states that: 'A review of the literature was conducted and leading lipodystrophy experts in the US, Brazil and Turkey were consulted.' However, no details of the search strategies used or inclusion/exclusion criteria for such a review were provided. In addition, it is unclear why only lipodystrophy experts in the US, Brazil and Turkey were contacted. The response to clarification questions[39] separately states that: 'The clinical SLR was carried out to search for trials of both metreleptin and trials of relevant comparators.' However, the search strategies described in section 17.1, appendix 1 of the CS[1] include lipodystrophy terms, which are combined with metreleptin terms using the AND function, i.e. these searches are not suitable for the identification of studies of the natural history of lipodystrophy syndromes or studies about interventions other than leptin replacement. In addition, the CS did not provide details of how unpublished studies were sought, for example was the UK treatment centre at Addenbrooke's Hospital approached form information? This information was requested in the clarification questions, but was not provided.

The company's response to clarification questions[39] included 23 spreadsheets and a document describing the natural history study.[40] The response to clarification questions includes the statement: 'Patients in the untreated sample were followed from birth while patients in the treated sample were first observed at the time of treatment. Additionally, two of the centers in the Natural History study also offered metreleptin treatment and appear to have preferentially selected patients with more severe symptoms for treatment. Therefore, the treated patients were, on average, at a more advanced stage of the disease at the start of observation compared to the untreated patients.' The baseline characteristics tables from the included metreleptin studies[37, 38] and the report of the natural history study[40] appear to support the view that patients in the treatment studies were at a more advanced stage of disease (see Tables 5, 6 and 8). However, the lack of clear information about which patients and results from the natural history study were used, in the CS means that it is impossible to adequately assess the extent to which it can provide a reliable comparison with data from the intervention studies.

The ERG recognises that no comparative studies of metreleptin versus standard care are available and that, in such cases, cost effectiveness analysis requires an indirect comparison between treatment and comparator studies. However, where indirect comparisons are used, it is essential that the same rigorous approach to identifying, selecting and reporting studies is applied for both intervention and comparator studies.

This is a major weakness of the CS which limits the interpretation of the available evidence.

3.3.4 Outcomes

The clinical effectiveness section of the CS focuses primarily on metabolic outcome measures; the CS includes no data or only very limited data for the clinical or patient-perceived outcomes specified in the NICE scope.[27] The protocols for both of the two studies included in the clinical effectiveness section of the CS list only metabolic and adverse events outcome measures;[37, 38] all other outcomes data appear to have been derived from publications of outcome data collected *ad hoc* by study investigators. No data are provided on liver cirrhosis, complications of diabetes, organ damage (including heart and kidneys) or effects on appearance. Mortality and pancreatitis are only reported where these are considered to be adverse effects of treatment or, in the case of pancreatitis, discontinuation of treatment.

3.3.5 Cost to the NHS and PSS, and value for money

The CS includes a cost effectiveness model in which the primary health outcome is valued in terms of incremental QALYs gained. In general, the scope was followed when assessing the costs of metreleptin to the NHS and the value for money it provides.

4 IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Section 9.1.1 of the CS states that a systematic literature review was undertaken to search for trials of metreleptin and trials of relevant comparators. Search strategies were reported in detail in Appendix 17.1. The search was conducted on 10 March 2017. The selection of databases searched was adequate (Ovid Medline and Medline in Process, EMBASE, and the Cochrane Library Databases) and all searches were clearly reported and reproducible, the database name, database date span, and date searched was provided for the majority of the searches. The service provider used to search the Cochrane Library was not provided, and the strategy for this database appeared incomplete, however, a complete version was provided in the company's response to clarification questions. No language or date limits were applied and the searches were not limited by study design so would capture both RCTs and non-randomised studies.

Additional searches in key international HTA websites (limited to Europe only), a number of relevant conferences and clinical trials registries were also undertaken, however more specific details of these searches were not provided in the CS (i.e. search terms, website details and results retrieved).

Internal sources at Aegerion Pharmaceuticals were also used to source ongoing clinical studies and unpublished clinical study reports.

The ERG ran a test strategy to investigate recall from searching for epidemiology and natural history studies along with more sensitive terms for the condition. The search retrieved 1,540 results. More details of this can be found in Appendix 1.

ERG comment:

- The search strategies did not include any search terms for comparators. Only studies for the intervention metreleptin would have been retrieved, natural history studies may have also been missed.
- The search strategies were well constructed with condition and intervention facets and contained a combination of subject heading index and free text terms. The majority of subject heading terms were unnecessarily exploded but this would not impact on results retrieved. The ERG also notes that there were broad search terms used for endocrine disease.
- The ERG noted that there were some additional terms for the condition that could have been added to the strategies to increase sensitivity, such as disease acronyms (FLP, FPLD2 etc.). The inclusion criteria lists additional condition terms not used in the search strategies such as the rare lipodystrophy syndromes, Donohue Syndrome, Wiedermann Rautenstrauch syndrome and Berardinelli-Seip Syndrome.
- The ERG feels that a search of additional grey literature sources such as the FDA could have retrieved further information of value, particularly regarding safety information published by the FDA regarding metreleptin.

- The grey literature searches (CS Appendix 17.1.5) in the company submission did not provide full details of the search terms used, the precise date of the searches or the number of records. It's not clear if the company searched for the condition or intervention or both in these resources, the ERG cannot therefore comment on the robustness of these searches.

4.1.2 Inclusion criteria

The eligibility criteria for the review are described in Table 2 (CS, Table C11, pages 68-69). The inclusion criteria are generally broad and aim to include all relevant intervention studies. The main problem, as described in section 3.3.3 above, is that no systematic process is reported for the identification and selection of comparator studies. In addition, a number of exclusion criteria are listed for population (HIV-associated LD, LD secondary to drug administration, LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections), which are not consistent with either the NICE scope.[27]

Table 2: Eligibility criteria

Inclusion criteria	
Population	Patients with congenital or acquired GL, in adults and children 2 years of age and above Patients with familial or acquired PL, characterised by leptin level <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA_{1c} ≥6.5 %, in adults and children 2 years of age and above Patients with rare LD syndromes (e.g. Donohue syndrome, mandibuloacral dysplasia (type A and type B) and Wiedemann Rautenstrauch syndrome), in adults and children 2 years of age and above
Interventions	Studies considering an interventional treatment
Outcomes	Clinical outcomes, including (not limited to): distribution of fat (% fat loss across face and neck, abdomen, thorax, upper limbs and lower limbs and number of fat sparing across face and neck abdomen, upper limb, lower limb, palms and soles), menstrual irregularities (polycystic ovaries etc.), hirsutism, growth, treatment related adverse events and mortality associated with LD and comorbidities associated with underlying disease Metabolic outcomes, including (not limited to): blood glucose (fasting glucose mg/dl), serum insulin (insulin (uIU/ml), HbA_{1c} %, lipid profile (triglycerides mg/dl, total cholesterol mg/dl, HDL-C mg/dl and LDL-C mg/dl), liver function tests (AST U/L, ALT U/L), alkaline phosphatase (U/L), blood urea nitrogen (mg/dl), creatinine (mg/dl) and leptin (ng/ml) Metabolic complications, including (not limited to): diabetes, hypertriglyceridemia, insulin resistance and acute pancreatitis Quality of life outcomes if measured within the trial, including standardised and non-standardised outcomes

Inclusion criteria	
Study design	RCTs, non-RCTs (e.g. single arm trials, real world/observational studies), pooled analyses, retrospective analyses, long-term extension phase studies, systematic reviews/meta-analyses Ongoing clinical studies and unpublished reports available internally at Aegerion Pharmaceuticals (unpublished)
Language restrictions	None
Search dates	Journal articles, reports and summaries: No restrictions Conference abstracts published within the last four years (January 2013-January 2017, inclusive)
Exclusion criteria	
Population	HIV-associated LD LD secondary to drug administration (insulin growth hormone, steroids, antibiotics and vaccinations) LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections LD in children <2 years of age
Interventions	Studies considering a non-interventional treatment
Outcomes	Studies reporting symptoms or short-term outcomes only Key search terms including: anatomy, histology, diagnosis, genetics, preclinical and reaction time
Study design	Phase 1 RCTs Study protocols Abstract with more recent existing full text publication Abstract or paper with insufficient reporting on population, study type or outcomes Healthy volunteer studies Animal studies Editorials/letters General reviews (other than systematic reviews)
Language restrictions	NA
Search dates	Conference abstracts published before 2013
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA_{1c}, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; HIV,Human immunodeficiency virus; LD, lipodystrophy; LDL-C, low density lipoprotein cholesterol; RCT, randomised controlled trial	

4.1.3 Critique of data extraction

The CS states that the process of study selection was made according to specifications in the protocol.[41] The following statement about study selection and data extraction methods is given in appendix 1 (CS, section 17.1.7, pages 223 to 224): 'All abstracts were reviewed by two experienced systematic review researchers; any difference in opinion regarding eligibility was resolved through discussion, using a third reviewer if necessary. The same process was applied to the subsequent review of full papers. Data were extracted from eligible publications into pre-defined tables by a researcher and verified against the original source paper by a second

researcher.'[1] This statement was repeated 10 times in succession, but no further details (e.g. a list of items to be extracted) were provided.

ERG comment: Although not clearly reported in the main body of the CS, the data extraction process seems to have been performed using standard systematic review methodology.[42]

4.1.4 Quality assessment

Each included study was critically appraised using criteria which the CS states were 'adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.'[1] No reference was provided and the critical appraisal presented (CS, Tables C20 and C21, pages 88 to 90) included only seven questions. When assessing methodological quality, it is generally preferable to use a published, validated risk of bias tool, appropriate to the study design being considered. In this case, the new Cochrane tool for assessing risk of bias in non-randomised intervention studies (ROBINS-I)[43] would have been an appropriate choice or, alternatively, the Newcastle-Ottawa scale for assessing the quality of non-randomised studies[44] could have been used. Further problems were that no information was provided about the number of reviewers involved in the critical appraisal process. Table C20, critical appraisal of study NIH 991265/20010769,[37] was incomplete in the CS;[1] a corrected version was supplied in the company's response to clarification questions.[39]

Economic evaluations were assessed using a checklist adapted according to Drummond and Jefferson (1996).[45]

ERG comment: There was a lack of information about the quality assessment process and published, validated Risk of Bias tools were not used to assess studies included in the clinical effectiveness section of the CS.

4.1.5 Evidence synthesis

The CS does not include any information about synthesis methods, however, the protocol for the systematic review linked to the CS[41] includes the following statement: 'The review will consist of data extraction and a narrative synthesis. No formal statistical analysis is planned.'

ERG comment: The ERG agrees with this approach.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

The systematic review conducted by the company identified 29 publications relating to metreleptin treatment for LD syndromes, which met the inclusion criteria listed in Table 2 above (CS, figure C14, page 70).

In total, the CS listed 16 publications relating to two eligible metreleptin interventional open label studies, the CSRs for which formed the basis of the clinical effectiveness section of the CS.[37, 38] The methodology and baseline participant characteristics for these two studies are described in detail in the CS (pages 73-85). Tables from the CS, describing study methods (Table 4) and baseline study characteristics (Tables 5 and 7), are reproduced below.

Study NIH 991265/20010769 (NCT00025883)[37] was an open-label, single-arm, investigator-sponsored study conducted at the NIH in the US between 2000 and 2014, with continuous enrolment and variable duration of follow-up; a follow-up study is ongoing.[46] The study aimed to investigate whether treatment with metreleptin could improve the metabolic sequelae, including pathological derangements in glucose and lipid homeostasis, found in patients with LD syndromes. Patients were enrolled from the US, countries in Europe including the UK, and other countries.

ERG comment: The response to clarification questions indicated that the CSR included only one patient from the UK.

Study NIH 991265 was a pilot, dose-escalation study to determine the safety and efficacy of short-term leptin replacement (up to eight months) and NIH 20010769 was conducted to determine the long-term safety and efficacy of metreleptin treatment for patients with LD. Study NIH 20010769 allowed for the rollover of patients from the pilot study, as well as for direct enrolment of new patients. Although conducted as separate studies, NIH 991265 and NIH 20010769 are treated, in the CS, as a single extended study since the two studies employed a similar protocol and all but one of the patients studied under the pilot study continued long-term treatment in the second study.[1, 47] Patients received self-administered or caregiver administered, subcutaneous metreleptin injections in one to two daily doses ranging from 0.06 to 0.24 mg/kg/day in study NIH 20010769 (0.01 to 0.08 mg/kg/day in study NIH 991265). Starting doses were dependent on age and gender, and doses were adjusted to achieve metabolic control and avoid excessive weight loss. Anti-hyperglycaemic and lipid-lowering regimens were modified if clinically indicated.[1, 37] The co-primary efficacy endpoints in this study were: actual change from baseline in HbA_{1c} at Month 12, and percent change from baseline in fasting serum triglycerides at Month 12.[1, 37] The study was conducted in the US where metreleptin was approved by the FDA in 2014. As of December 2014, all patients were either off metreleptin treatment or had transitioned to commercial product or free-drug programmes.[1, 37] The CSR for this study was based on all available data from the final integrated analysis on all patients (n=107) over the 14-year development period of metreleptin.[1, 37]

Study FHA101 was an open-label, expanded access study designed to provide metreleptin for the treatment of patients with diabetes mellitus and/or hypertriglyceridemia associated with LD. The study was initiated in 2008 in the US and all patients were enrolled from the US. As with study NIH991265/ 20010769, as of December 2014, all patients were either off metreleptin treatment or had transitioned to commercial product or free-drug programmes.[1, 38] Patients or caregivers injected metreleptin subcutaneously at 0.02 mg/kg twice daily (BID) for one week, modified to one month in June 2009, followed by 0.04 mg/kg BID.[1, 38] Dosage adjustments were allowed based on patient response. Dose titration up to 0.08 mg/kg BID was allowed if there were no improvements in metabolic parameters, and a reduction in target dose was permitted if tolerability became an issue. If metabolic parameters were stabilised after one year of treatment, then a decrease in dosing frequency from BID to once daily was allowed. Patients continued concomitant glucose-and lipid-lowering medications after the baseline visit, and further adjustments were permitted at the discretion of the treating physician.[1, 38] Patients

met with their treating physician one week after the first treatment and monthly for the first three months, followed by every three months throughout the first year. Following one year of treatment, patient visits were scheduled every six months or more frequently as deemed appropriate by the investigator. [1, 38]

The NIH991265/ 20010769 study included a much higher proportion of participants with GL, 66/107 (62%) than the FH101 study, 9/41 (22%). In study NIH 991265/20010769 the median age of the GL group was 15 years with 68% of patients <18 years of age; patients in the PL subgroup were older (median age 38 years) than those in the GL group, with 84% ≥18 years of age.[1] In study FHA101 most patients in both groups were ≥18 years of age at the time of enrolment.[1] In general, the baseline metabolic measures for patients in study FHA101 were not as elevated as those for patients in study NIH 991265/20010769 (see Tables 5 and 7 below).

Nine publications[48-56] were listed in Table C13 (CS, page 72) as 'excluded published studies.' The reason given for exclusion was: 'These studies were not included in the EMA (or the FDA) application; they only include a small number of patients and/or a population not relevant to this submission e.g. Japanese patients and/or PL patients who are not specific to the sought after indicated population.'[1]

ERG comment: The number of studies listed in tables C12 and C13 (CS, pages 71-72), does not match the total given in the PRISMA flow diagram (figure C14, CS, page 70). In addition, the exclusion of the studies listed in Table C13 (CS, page 72) is not consistent with the NICE scope[27] or with the pre-specified inclusion/exclusion criteria for the systematic review (see Table 2 above). The arbitrary exclusion of studies, based on small sample size, is particularly problematic in the context of summarising the evidence about an ultra-rare condition. Of particular note is the study by Simha et al. 2012,[50] which assessed the effects of leptin therapy in 24 female patients with Dunnigan variety FPL and moderate or severe hypoleptinemia and found no significant change from baseline to six months in fasting glucose, insulin, glucose tolerance, or HbA_{1c} levels.

The company provided a revised table of included/excluded studies in their response to clarification questions (Table 3, below). Although this table provides some further information on the reasons for excluding studies, it does not provide any reasons that are consistent with the pre-specified inclusion/exclusion criteria. The two publications, relating to one systematic review and listed in Table 3, were mentioned in the CS (section 9.2.2, page 69), but no references were provided; copies of the articles were not provided in either the CS or the response to clarification questions.

One included article, Oral et al. 2006[57] reported outcomes (circulating lymphocytes and cytokine response) which were not listed in the CSR for NIH 991265/20010796.[37]

Based on the PRISMA flow diagram (Figure C14, CS, page 71), 31 articles were excluded at the full text screening stage; details of these articles were not provided.

The CS does not include a description of the methods or baseline participant characteristics of the 'GL/PL natural history study', which was used to provide comparator data for the cost effectiveness modelling. A summary of the study protocol and baseline participant characteristics were provided in the company's response to clarification questions, and these are reproduced in Tables 8 and 9, below.[40] Table 9 provides details of those baseline participant characteristics that were also reported in the CS for the two metreleptin studies, NIH 991265/20010796 and FH101 or which were available from the NIH follow-up study,[46] (see Table 6). We have included these details in our report in order to allow a crude comparison to be made between the treatment studies included in the CS and the GL/PL study. As noted in the CS, participants in the GLPL natural history study had generally lower levels of HbA_{1c} and triglycerides than those in the metreleptin treatment studies. Of further note is the high proportion (approximately 50%) of participants in the GL/PL natural history study who were of Turkish ethnicity. The matching exercise outlined in section 17.6.2, Appendix 6, pages 270-271 of the CS, does not indicate that either ethnicity or baseline metabolic measures were considered when matching participants from the NIH follow-up study[46] to participants from the GL/PL natural history study.[40] Definitions of organ damage differed between the NIH follow-up study[46] and the GL/PL natural history study,[40] and the proportion of patients with liver, kidney or heart damage at baseline, or with a history of pancreatitis was generally lower in the GL/PL natural history study than in the NIH follow-up study. This may be because the metreleptin intervention study included patients who were at a later stage of LD than the GL/PL natural history study, where the baseline period is defined as the time before first GL/PL diagnosis.[40]

Table 3: Publications identified by the systematic literature view and their inclusion or exclusion in the submission (reproduced from the company's response to clarification questions

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Metreleptin studies				
NIH 991265/20010796 (NCT00025883)				
Oral et al. 2002[58] Full publication	Prospective, open-label, single arm (4 months)	Patients with various forms of LD (N=9)	To determine whether leptin replacement improves the insulin resistance, diabetes, and hypertriglyceridemia of patients with LD	Study NIH 991265/20010769 was used to inform the clinical effectiveness and safety of metreleptin. Overall 16 published studies relating to this study were identified in the SLR However, the studies were (mostly) not specifically described in the submission. They were published while the study was ongoing and thus report on fewer patients than in an integrated CSR, which has been provided by Aegerion. The integrated CSR includes data from 107 LD patients (GL=66; PL=41; PL subgroup=31) and therefore is more statistically robust than these individual studies. A follow-up to this study (NIH-follow-up study) was used to inform the economic model.
Petersen et al. 2002[59] Full publication	Case control (3-8 months)	Patients with severe GL (fasting leptin concentration less than 4 ng/ml) associated with diabetes (N=3)	To examine whether or not leptin treatment might improve insulin sensitivity in LD patients	
Javor et al. 2005a[60] Full publication	Prospective, open-label, single arm (12 months)	GL patients (N=15)	To determine the long-term effects of leptin replacement in a cohort of LD subjects	
Oral, et al. 2006[57] Full publication	Prospective, open-label, single arm (4-8 months)	Patients with various forms of LD (N=10)	To study lymphocyte subpopulations and in vitro peripheral blood mononuclear cell activation during a study evaluating the effects of leptin on metabolic functions in severe LD (serum leptin levels <4 ng/ml).	
Musso, et al. 2005[61] Full publication	Prospective, open-label, single arm (8-12 months)	Patients with various forms of LD (N=14)	(a) Investigated the role of recombinant leptin therapy on the hyperandrogenic state and menstrual dysfunction of patients up to 1 year of treatment; (b) evaluated the effect of	

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
			metreleptin on the growth hormone (GH) and insulin-like growth factor 1 (IGF-1) axis; (c) evaluated the pituitary-adrenal and thyroid axis over a 1-year period of metreleptin therapy; and (4) evaluated the effect of metreleptin therapy on the pituitary gonadal axis in a few male subjects to complement recent studies in male normal volunteers	
Park et al. 2007[62] Full publication	Prospective, open-label, single arm (12 months)	Patients with FPLD (N=6)	To investigate the role of low-dose recombinant leptin therapy in patients with FPLD to determine (1) the response of metabolic parameters to treatment, (2) the safety and tolerability of treatment over the long term, and (3) the differences of metabolic parameters at baseline and in response to treatment in patients with FPLD and GL.	
Chan et al. 2011[37] Full publication	Prospective, single-arm, open-label (12 months, but ongoing. Some patients have received up to 9 years of treatment up to July 2009 data cut)	Patients with acquired or inherited LD (N=55)	Evaluate the safety and effectiveness of leptin replacement therapy in patients with LD	

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Joseph et al. 2014[63] Full publication	Prospective, single-arm, open-label (24 months)	Patients with various forms of LD (N=82)	To study the effects of metreleptin in TGs and HDL in LD in contrast to changes in TGs and HDL in interventions for the obesity-associated metabolic syndrome	
Christensen et al. 2014[64] Full publication	Prospective, single-arm, open-label (96-120 months)	Patients with CGL (N=31)	To study the effects of metreleptin on bone mineral content and mineral metabolism	
Chong et al. 2010[65] Full publication	Prospective, single-arm, open-label (96 months: metabolic outcomes at 12 months reported)	Patients with GL or PL (acquired or inherited) (N=48)	To determine whether leptin replacement in LD patients ameliorates their metabolic abnormalities over an extended period of time and whether leptin therapy is effective in the different forms of LD	
Brown et al. 2013[66] Abstract	Prospective, single-arm, open-label (12 months but on-going; as of a July 2011 data cut, treatment duration was 2 month to 11 years including 64 patients treated for approximately	Patients with various LD subtypes (CGL, FPL, AGL, APL) (N=64)	To examine the effect of metreleptin on achieving commonly accepted therapeutic targets for HbA_{1c} and TG reduction at a 12-month treatment time point	

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
	12 month or more)			
Muniyappa et al. 2013[67] Full publication	Prospective, single-arm, open-label (16-20 weeks)	Congenital or acquired LD (N=13)	To examine the early effects (16–20 weeks) of leptin replacement on B-cell function in patients with LD	
Diker-Cohen et al. 2015[19] Full publication	Prospective, open-label, single arm (12 months, but ongoing. Some patients have received up to 9 years of treatment up to July 2009 data cut)	GL or PL (N=86)	Evaluate the safety and effectiveness of leptin replacement therapy in patients with GL and PL	
Moran, et al. 2004[68] Full publication	Prospective, open-label, single arm (12 months)	Patients with various forms of LD (N=14)	To determine the effect of leptin replacement therapy in patients with LD on (1) body composition, comprising changes in fat and lean body mass and (2) bone density and serum markers of bone metabolism. In addition, the effects on liver volume and resting energy expenditure were determined	The study by Moran was used in Section 9.6.1.4.4 Effect of metreleptin on hyperphagia (CS, page 99) "As reported by Moran and colleagues from the NIH, metreleptin treatment of 14 patients with LD (12 with GL and 2 with PL) dramatically decreased food intake at 4 months from 3,170 kcal/day to 1,739 kcal/day."

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Safar Zadeh et al. 2013[24] Full publication	Prospective, single-arm, open-label (Mean: 26 months; median 15 months, range 4–68 months)	Patients with GL or PL (N=27)	To study the spectrum of liver disease in LD and the effects of leptin replacement	The study by Safar-Zaheh was used in Section 9.6.1.4.3: Effect of metreleptin on hepatic enzymes, liver volume, and liver pathology (CS, page 98)
Javor et al. 2005b[69] Full publication	Prospective, open-label, single arm (Mean 6.6 [range: 4-18] months)	GL (8 patients) or FPLD (2 patients) (N=10)	To examine the prevalence of NASH in LD patients with steatosis and to assess the histological changes in the context of biochemical and radiographic changes seen with metreleptin therapy.	The results of the study by Javor were not specifically included in the submission; however it showed that metreleptin significantly reduced triglycerides, transaminases, hepatomegaly, and liver fat content. These reductions were associated with significant reductions in steatosis and the hepatocellular ballooning injury seen in NASH.
FHA101 (NCT00677313)				
Ajluni et al. 2016[70] Full publication	Prospective, single-arm, open-label (expanded access) (12 months)	Patients with PL and diabetes and/or hypertriglyceridemia with no pre-specified leptin level (N=23)	To determine the efficacy and safety of metreleptin among patients with PL using an expanded-access model	Study FHA101 was used, in the CS, as supportive evidence of the clinical effectiveness and safety of metreleptin. One publication relating to FHA101 was identified.[70] However, the study not specifically described in the submission. Instead the integrated CSR, provided by Aergerion was used. includes data from 41 patients (GL= 9; PL=32; PL subgroup=7)

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Metreleptin studies identified in the SLR but not included in the submission (with reason for exclusion)				
Beltrand et al. 2007[48] Full publication	Prospective, open-label, single arm (4 months)	Children with BSCL (N=7)	To test safety and efficacy of metreleptin treatment in children with BSCL before development of severe metabolic disease	Small sample size, short duration (4 months) study, only conducted in children (age range: 2.4-13.6 years)
Beltrand, et al. 2010[49] Full publication	Prospective, open-label, single arm (28 months)	Children with BSCL (N=8)	To assess the long-term efficacy and safety of leptin-replacement therapy to correct for the metabolic disorders.	Small sample size, only conducted in children (included 7 children from the above, short term trial).
Simha, et al. 2012[50] Full publication	A parallel group, open-label, observational study (6 months)	FPLD2 patients (N=24)	To compare efficacy of leptin therapy in FPLD patients with SH (serum leptin 7th percentile of normal) vs. those with moderate hypoleptinaemia (MH; serum leptin in 7th to 20th percentiles).	Small sample size only in patients with familial PL
Asthana, et al. 2015[51] Abstract	Prospective, open-label, single arm (16-32 weeks [4-8 months])	GL (N=9) or PL (N=8) (N=17)	To compare plasma angiopoietin-like protein 3 (ANGPTL3) and 4 in patients with LD and healthy controls and b) to examine the effects (16–32 weeks) of leptin replacement on ANGPTL 3 and 4	Small sample size, only an abstract (lack of information)
Brown, et al. 2015[52] Abstract	Non-randomised crossover study (19 days)	Previously leptin-treated (N=5, all GL, treatment duration 1-12y) and leptin-naïve (N=10, 9 PL) subjects (N=15)	To determine if leptin improves glucose and lipid metabolism in LD, independent of its effects on food intake.	Small sample size, only an abstract (lack of information)

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Ebihara, et al. 2007[53] Full publication	Prospective, open-label, single arm (36 months)	GL patients (Japanese) (N=7)	To evaluate the efficacy and safety of long-term leptin-replacement therapy on seven Japanese patients with generalised LD.	Small sample size in Japanese patients (i.e different ethnic population than expected in the UK)
Schlogl, et al. 2016[54] Full publication	Prospective, open-label, single arm (52 weeks [12 months])	Patients with GL or PL (N=9)	Resting state functional MRI scans and extensive behavioural testing assessing changes in hunger/satiety regulation were performed during the first 52 weeks of metreleptin treatment in nine patients with LD	Small sample size
Vatier, et al 2016[55] Full publication	Prospective, open-label, single arm (compassionate therapeutic programme) (12 months)	Patients with various forms of LD (N=16)	To evaluate the effect of metreleptin on insulin sensitivity and insulin secretion using dynamic IV clamp procedures in 16 patients with genetic LD syndromes, included in a compassionate therapeutic programme	Small sample size
Araujo-Vilar, et al. 2015[56] Full publication	Retrospective, open-label study, single arm (Median 3 years [range 9 months to 5 years, 9 months])	Patients with genetic LD syndromes (N=9)	To determine the effectiveness of recombinant methionyl leptin (metreleptin) for improving glucose metabolism, lipid profile, and hepatic steatosis in patients with genetic lipodystrophy syndromes	Small sample size

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Rodriguez, et al. 2014[71] Full publication	SLR and meta-analysis	LD not associated with the use of HIV protease inhibitors	A systematic review of the MEDLINE and Cochrane Library databases was conducted to identify studies assessing the effect of metreleptin on metabolic and hepatic endpoints of patients with lipodystrophy not associated with the use of HIV protease inhibitors	Systematic reviews were an inclusion criteria in the clinical SLR. Two publications from the same group reported the results of a systematic review and meta-analysis into the effects of metreleptin on metabolic and hepatic endpoints in patients with lipodystrophy syndromes not associated with the use of HIV protease inhibitors. In the full-text article by Rodríguez et al. 2014, 12 studies were included after full-text review of the papers identified in their literature search of Medline and the Cochrane library. All of these papers have been included in the current SLR reported here i.e. Beltrand et al. 2007 and 2010; Chan et al. 2011; Chong et al. 2009; Ebihara et al. 2007; Javor et al. 2005b; Moran et al. 2004; Oral et al. 2002; Park et al. 2007; Petersen et al. 2002; Safar Zadeh et al. 2013; and Simha et al. 2012. In the abstract by Paz-Filho et al. 14 studies were identified (the details were not reported). The results of the systematic review and meta-analysis were not considered relevant to the submission due to some limitations. In Rodríguez et al. a meta-analysis of results (N=226 patients across the studies)showed
Paz-Filho, et al. 2014[72] Abstract	SLR and meta-analysis	LD not associated with the use of HIV protease inhibitors	A systematic review of the MEDLINE and Cochrane Library databases was conducted to identify studies assessing the effect of metreleptin on metabolic and hepatic endpoints of patients with LD not associated with the use of HIV protease inhibitors	

Publication	Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
				that metreleptin decreased FPG (0.75 standardised mean differences [SMD] units [range 0.36-1.13], P = 0.0001), HbA_{1c} (0.49 [0.17-0.81], P = 0.003), triglycerides (1.00 [0.69-1.31], P < 0.00001), total cholesterol (0.62 [0.21-1.02], P = 0.003), liver volume (1.06 [0.51-1.61], P = 0.0002) and AST (0.41 [0.10-0.73] P =0.01). However, the review has several limitations, particularly that several of the studies from NIH 991265/20010796 were included individually but they may have included some of the same patients. In Paz-Filho et al. a meta-analysis of results from clinical studies in 243 patients showed that metreleptin decreased FPG [0.76 SMD units (range 0.40-1.12), P < 0.0001], HbA_{1c} [0.55 (0.23-0.86), P = 0.0006], triglycerides [1.12 (0.81-1.43), P < 0.00001], total cholesterol [0.62 (0.21-1.02), P = 0.003), liver volume [0.98 (0.52-1.43), P < 0.0001], liver fat [0.67 (0.44-0.89), P < 0.0001], ALT [0.44 (0.07-0.80), P = 0.02] and AST [0.45 (0.17-0.73) P = 0.002].

Publication		Study design (treatment duration)	Population	Objective	Inclusion or exclusion in the submission
Comparator study					
29	Dantas de Medeiros Rocha, et al. 2010[73] Full publication	Prospective, open-label, single arm	BSCL patients (N=10)	To evaluate the effect of diet intervention and oral zinc supplementation on the metabolic control of BSCL patients	This study was not considered suitable for the submission because oral zinc supplementation is not established clinical management for the treatment of LD, together with the study limitations i.e small sample size and short treatment duration.

Abbreviations: AGL = acquired generalised lipodystrophy; APL = acquired partial lipodystrophy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSCL = Berardinelli-Seip congenital lipodystrophy (also known as CGL); CGL = congenital generalised; CSR = clinical study report; FPG = fasting plasma glucose; FPL = familial partial lipodystrophy; FPLD = familial partial lipodystrophy, Dunnigan variety; GL = generalised lipodystrophy; HDL = high-density lipoprotein-cholesterol; IV = intravenous; LD = lipodystrophy; MRI = magnetic resonance imaging; MH = moderate hypoleptinaemia (serum leptin in 7th to 20th percentiles); NASH = non-alcoholic steatohepatitis; PL = partial lipodystrophy; Pts = patients; SD = standard deviation; SH = severe hypoleptinaemia (serum leptin 7th percentile of normal); SMD = standardised mean differences; TG = triglycerides

Table 4: Summary of study methods, reproduced from Table C15 (CS, pages 77-80)

Study name	NIH 991265/20010769
Objective	To evaluate the safety and efficacy of recombinant methionyl human leptin (metreleptin) replacement in patients with GL and PL
Location	The studies were conducted at the NIH, however patients were also enrolled from countries outside the US: GL: 59% were from the US; 20% from Europe/Eastern Mediterranean (Belgium, UK, Germany, Italy, Lithuania, Spain, Turkey, Albania, Israel, and Serbia); 18% from other countries.* PL: 78% from the US, 7% from Europe/Eastern Mediterranean; 15% from other countries*
Design	Open-label, single-arm
Duration of study	Continuous enrolment over 14 years (2000-2014): NIH 991265: 8 months NIH 20010769: Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months
Patient population	Patients with GL or PL
Sample size	N=107 (GL=66; PL=41; PL subgroup=31)*
Inclusion criteria	Age: Study NIH 2001769: 6 months; Study NIH 991265: >5 years Clinically significant LD identified as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient Circulating leptin levels: Study NIH 2001769: <12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years; Study NIH 991265: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males Presence of at least 1 of the following metabolic abnormalities: • Presence of diabetes mellitus • Fasting insulin concentration >30 μU/mL (208.4 pmol/L) • Fasting triglyceride concentration >200 mg/dL (>2.26 mmol/L), or postprandially elevated triglyceride concentrations Triglyceride concentration >500 mg/dL (>5.65 mmol/L) when fasting is not clinically indicated (e.g., infants)b
Exclusion criteria	General: Pregnant women, women in their reproductive years who did not use an effective method of birth control, and women who were nursing or who were lactating within 6 weeks of having completed nursing. Exclusions for underlying disease likely to increase side effects or to hinder objective data collection: • Known infectious liver disease (in Study NIH 99165, known liver disease due to causes other than NASH) • Known human immunodeficiency (HIV) infection • Current alcohol or substance abuse • Psychiatric disorder impeding competence or compliance • Active tuberculosis • Use of anorexigenic drugs

	• Other condition(s) that in the opinion of the clinical investigators would impede completion of the study • Patients who have a known hypersensitivity to Escherichia coli-derived proteins
Statistical tests*	The primary and key secondary efficacy analyses were performed primarily on the FAS (all patients who received at least 1 dose of study drug and had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit). The primary and key secondary endpoints were summarised using descriptive statistics and 95% CIs. P values for the primary endpoints were computed using paired t-tests to determine if the change from baseline to Month 12 was significantly different from 0, at a one-sided α-level of 0.025. The LOCF method was used to impute any missing Month 12 results. The imputation only took into account results that were at least 6 months (180 days) post-baseline. Thus, the analysis included all patients that had baseline and at least Day 180 measurements. A MMRM analysis was used to assess changes over time for the entire duration of the study.
Primary outcomes	• Actual change from baseline in HbA_{1c} at Month 12 • Percent change from baseline in fasting serum triglycerides at Month 12
Key secondary outcomes	Proportion of patients achieving target actual decreases of: • ≥1% decrease in HbA_{1c} or ≥30% decrease in fasting serum triglycerides at Month 12 • ≥1.5% decrease in HbA_{1c} or ≥35% decrease in fasting serum triglycerides at Month 12 • ≥2% decrease in HbA_{1c} or ≥40% decrease in fasting serum triglycerides at Month 12 • Actual and percent change from baseline in fasting plasma glucose levels at Month 12
Other relevant secondary outcomes	• Actual change from baseline in HbA_{1c} at each post-baseline visit • Percent and actual change from baseline in fasting serum triglycerides at each postbaseline visit • Actual and percent change from baseline in fasting lipids (total cholesterol, LDL-C, HDL-C) through Month 12 • Actual change from baseline in ALT and AST at each post-baseline visit through Month 12 • Actual change from baseline in liver volume at each post-baseline visit through Month 12
Other endpoints of relevance	• Assessment of concomitant medications • Adverse events (including deaths, and cases of pancreatitis and infections) • Growth and pubertal status • Liver volume and pathology: Ultrasound of the liver and, if abnormalities are found, possibly liver biopsies
Study name	**FHA101**
Objective	To provide expanded access to metreleptin to patients with LD and associated metabolic disorders such as diabetes mellitus and/or hypertriglyceridemia and to test the safety and efficacy of metreleptin in this population of patients.
Location	Six centres in the US*

Design	Open-label, expanded-access
Duration of study	Continuous enrolment over 6 years (2008-2014)*: Primary endpoint evaluated at 12 months; longer-term efficacy data presented at 36 months
Patient population	Patients with GL or PL (including subgroup of PL patients with baseline leptin <12 ng/mL and HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L)
Sample size	N=41 (GL= 9; PL=32; PL subgroup=7)*
Inclusion criteria	Male or female ≥5 years old Physician-confirmed LD as defined by evidence of generalised (whole body) or partial (limbs) loss of body fat outside the range of normal variation Diagnosed with at least 1 of the following 2 metabolic disorders: • Diabetes mellitus • Hypertriglyceridemia as defined by fasting triglyceride concentrations >2.26 mmol/L (>200 mg/dL)
Exclusion criteria	Diagnosed with human immunodeficiency virus (HIV) infection Clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the Investigator Acquired LD and clinically significant haematologic abnormalities (such as neutropaenia and/or lymphadenopathy) Known infectious liver disease Known allergies to E. coli-derived proteins or hypersensitivity to any component of study treatment
Statistical tests*	The primary and key secondary efficacy analyses were performed primarily on the FAS (all patients who received at least 1 dose of study drug and had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit). The primary and key secondary endpoints were summarised using descriptive statistics and 95% CIs. P values for the primary endpoints were computed using paired t-tests to determine if the change from baseline to Month 12 was significantly different from 0, at a one-sided α-level of 0.025. The LOCF method was used to impute any missing Month 12 results. The imputation only took into account results that were at least 6 months (180 days) post-baseline. Thus, analysis of primary efficacy endpoints included all patients that have baseline and at least Month 6 measurements. A MMRM analysis was used to assess changes over time for the entire duration of the study.
Primary outcomes	• Actual change from baseline in HbA_{1c} at Month 12 • Percent change from baseline in fasting serum triglycerides at Month 12

Key secondary outcomes	Proportion of patients achieving target actual decreases of: • ≥1% actual decrease in HbA_{1c} or ≥30% decrease in fasting triglycerides at Month 12 • ≥1.5% decrease in HbA_{1c} or ≥35% decrease in fasting triglycerides at Month 12 • ≥2% actual decrease in HbA_{1c} or ≥40% decrease in fasting triglycerides at Month 12 • Actual and percent change from baseline for fasting glucose levels at Month 12
Other relevant secondary outcomes	• Actual change from baseline in HbA_{1c} at each post-baseline visit • Percent and actual change from baseline in fasting serum triglycerides at each postbaseline visit • Actual change from baseline in ALT and AST at each post-baseline visit through Month 12

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; FAS, full analysis set; FFA, free fatty acid; GL,generalised lipodystrophy; HbA_{1c}, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; HIV, human immunodeficiency virus; LD, lipodystrophy; LDL-C, low density lipoprotein cholesterol; LOCF, last observation carried forward; MMRM, Mixed-effect Model Repeated Measures; NASH, non-alcoholic steatohepatitis; NIH, National Institutes of Health; PL, partial lipodystrophy; UK, United Kingdom; US, United States

[a] PL subgroup = patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] Inclusion criteria for study NIH 20010769 (but not NIH 991265)

Table 5: Baseline characteristics for study NIH 991265/20010769, reproduced from Table C16 (CS, page 82)

Characteristic	GL (N = 66)	PL (N = 41)	
		PL subgroup[a] (N = 31)	Overall (N = 41)
Female, n (%)	51 (77.3)	30 (96.8)	40 (97.6)
Race, n (%)			
Caucasian	31 (47.0)	26 (83.9)	36 (87.8)
Black	16 (24.2)	0	0
Asian/Native American/Hispanic/Other	3 (4.5)/ 2 (3.0)/ 11 (16.7)/ 3 (4.5)	1 (3.2)/ 0 / 2 (6.5)/ 2 (6.5)	1 (2.4)/ 0/ 2 (4.9)/ 2 (4.9)
Age, years, median (range)	15.0 (1.0, 68.0)	38.0 (15.0, 64.0)	34.0 (10.0, 64.0)
<18 years	45 (68.2)	5 (16.1)	8 (19.5)
≥18 years	21 (31.8)	26 (83.9)	33 (80.5)
LD type, n (%)			
Acquired	21 (31.8)	4 (12.9)	6 (14.6)
Congenital/Familial	45 (68.2)	27 (87.1)	35 (85.4)
Fasting leptin, ng/ml, median (range)	1.0 (0.2, 5.3)	5.9 (1.6, 16.9)	5.9 (1.0, 16.9)
BMI, kg/m^2, median (range)	20.5 (14.0, 29.5)	25.1 (18.6, 33.3)	25.3 (17.7, 33.3)
HbA_{1c}, %			
Median (range)	8.7 (4.5, 13.7)	8.6 (5.7, 13.3)	7.8 (4.6, 13.3)
≥6.5, n (%)	49 (74.2)	29 (93.5)	29 (70.7)
≥8.0, n (%)	42 (63.6)	19 (61.3)	19 (46.3)
Fasting plasma glucose, mmol/L, median (range)	10.3 (5.04)	9.9 (4.33)	8.7 (4.35)
Fasting triglycerides, mmol/L			
Median (range)	14.5 (25.29)	14.8 (25.72)	12.0 (22.85)
≥2.26 mmol/L	50 (75.8)	27 (87.1)	34 (82.9)
≥5.65 mmol/L	26 (39.4)	15 (48.4)	15 (36.6)
ALT, >ULN, n (%)	49 (74.2)	9 (29.0)	14 (34.1)
AST, >ULN, n (%)	36 (54.5)	7 (22.6)	10 (24.4)
Anti-diabetic medications at baseline, n (%)	53 (80.3)	30 (96.8)	37 (90.2)
Lipid-lowering medications at baseline, n (%)	34 (51.5)	26 (83.9)	34 (82.9)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GL, generalised lipodystrophy; HbA_{1c}, glycated haemoglobin; LD, lipodystrophy; PL, partial lipodystrophy; ULN, upper limit of normal

[a] PL subgroup, patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

ERG comment: Additional baseline lipodystrophy characteristics were reported in the NIH follow-up study,[46] for the 107 patients originally included in the NIH 991265/20010769 study

and an additional five patients. These data were not included in the CS, but are recorded in Table 6, below.

Table 6: Baseline lipodystrophy characteristics for the NIH follow-up study population, including the 107 participants in the NIH 991265/20010769 study

Characteristic	All patients N=112 (93 F, 19 M)	GL patients N=68 (51F, 17M)	PL patients N=44 (42 F, 2M)
Impaired physical appearance	86 (77%)	56 (82%)	30 (68%)
Disruption to female reproductive system	45 (80%)	21 (78%)	24 (83%)
Heart abnormality	50 (45%)	36 (53%)	14 (32%)
Hyperphagia	88 (79%)	57 (84%)	31 (70%)
Kidney abnormality	71 (63%)	46 (68%)	25 (57%)
Liver abnormality	105 (94%)	63 (93%)	42 (95%)
Pancreatitis	44 (39%)	21 (31%)	23 (52%)
Unable to attend school or perform work	48 (43%)	39 (57%)	9 (20%)
Impaired physical appearance is determined by the presence of acanthosis nigricans, hyperkeratosis, or hirsutism. Disruption to female reproductive function is determined by the presence of irregular menstruation or polycystic ovary syndrome (PCOS). Heart abnormality includes hypertrophy, any dilation, any regurgitation, cardiomyopathy, and tachycardia. Hyperphagia is determined by notes in the medical charts. Kidney abnormality includes proteinuria, enlarged kidneys, nephropathy, hydronephrosis, renal disease, nephromegaly, renal failure, renal calculus, and glomerulosclerosis. Liver abnormality includes hepatomegaly, any form of fatty liver or steatosis, fibrosis, cirrhosis, and hepatitis. A patient is considered to have pancreatitis at baseline if the patient has ≥1 episodes of pancreatitis in the one year prior to metreleptin initiation. Loss of ability to perform work/school work is defined as incomplete school attendance due to disease symptoms for school age patients or not working/working part-time due to disease symptoms			

Table 7: Baseline characteristics for study FH101, reproduced from Table C17 (CS, page 83)

Characteristic	GL (N = 9)	PL (N = 32)	
		PL subgroup[a] (N = 7)	Overall (N = 32)
Female, n (%)	8 (88.9)	7 (100.0)	31 (96.9)
Race n (%)			
Caucasian	8 (88.9)	5 (71.4)	22 (68.8)
Black	1 (11.1)	2 (28.6)	3 (9.4)
Asian/Native American/Hispanic/Other	0/0/0/0	0/0/0/0	1 (3.1)/ 2 (6.3)/ 1 (3.1)/ 3 (9.4)
Age, median (range)	25.0 (9.0, 67.0)	42.0 (23.0, 57.0)	44.5 (23.0, 67.0)
<18 years	3 (33.3)	0	0
≥18 years	6 (66.7)	7 (100.0)	32 (100.0)
LD type			

Characteristic	GL (N = 9)	PL (N = 32)	
		PL subgroup[a] (N = 7)	Overall (N = 32)
Acquired	6 (66.7)	1 (14.3)	3 (9.4)
Congenital/Familial	2 (22.2)	6 (85.7)	29 (90.6)
BMI, kg/m^2, median (range)	21.3 (13.9, 38.4)	27.6 (20.9, 30.5)	30.3 (19.1, 41.2)
HbA_{1c}, %			
Median (range)	8.4 (5.1, 10.2)	7.6 (5.7, 11.1)	8.0 (5.6, 12.8)
≥6.5, n (%)	6 (66.7)	6 (85.7)	27 (84.4)
≥8.0, n (%)	5 (55.6)	2 (28.6)	16 (50.0)
Fasting plasma glucose, mmol/L, median (range)	10.4 (4.2, 23.3)	7.4 (5.1, 13.4)	7.8 (2.0, 15.0)
Fasting triglycerides, mmol/L,			
Median (range)	3.3 (1.5, 119.9)	2.9 (0.7, 14.0)	3.2 (0.7, 50.4)
≥2.26 mmol/L	6 (66.7)	4 (57.1)	23 (71.9)
≥5.65 mmol/L	3 (33.3)	1 (14.3)	7 (21.9)
ALT, >ULN, n (%)	5 (55.6)	5 (71.4)	23 (71.9)
AST, >ULN, n (%)	4 (44.4)	2 (28.6)	9 (28.1)
Anti-diabetic medications at baseline, n (%)	2 (22.2)	6 (85.7)	19 (59.4)
Lipid-lowering medications at baseline, n (%)	2 (22.2)	6 (85.7)	19 (59.4)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; GL = generalised lipodystrophy; LD = lipodystrophy; HbA_{1c} = glycated haemoglobin; PL = partial lipodystrophy; ULN = upper limit of normal

[a]PL subgroup = patients with baseline leptin <12 ng/mL and HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

Table 8: Protocol synopsis for the GL/PL natural history study, reproduced from an unpublished report included in the company's response to clarification questions

Study rationale	Generalized lipodystrophy (GL) and partial lipodystrophy (PL) are ultra-rare conditions associated with partially or fully absent adipose tissue, respectively. With fat accumulating in non-adipose tissue, GL and PL can lead to physical irregularities, organ damage. More research is needed to understand the natural history, including organ damage and mortality, of patients with GL and PL.
Objectives	1. To describe the demographic and clinical characteristics of metreleptin-naïve patients with GL and PL 2. To describe time to organ damage and time to disease progression of metreleptin-naïve patients with GL and PL 3. To describe the overall survival of metreleptin-naïve patients with GL and PL
Study Measures and Outcomes	Study measures included: - Patient demographic characteristics as of diagnosis of GL or PL (**Objective 1**) - Type of lipodystrophy diagnosed (i.e., phenotype and genotype) (**Objective 1**) - Patient physical characteristics and vital signs during patient's lifetime (**Objective 1**) - Laboratory values during patient's lifetime (**Objective 1**) - Organ damage during patient's lifetime (**Objective 2**)

	- Complications and comorbidities during patient's lifetime (**Objective 1**) - Mortality and causes of death (**Objective 3**) Disease progression was defined as the onset of a second organ damage following prior damage in a different organ. (**Objective 2**)
Data Sources	Data extracted from medical charts from five leading treatment centers for GL and PL across three countries (Brazil, Turkey, and the United States). These include: - United States (data collection complete) 1. National Institutes of Health (Rebecca Brown, MD, MHSc) 2. University of Michigan (Elif Oral, MD) - Turkey (data collection complete) 3. Dokuz Eylul University Medical School (Baris Akinci, MD) - Brazil (ongoing data collection) 4. Universidade de São Paulo – Campus Ribeirão Preto (Maria Cristina Foss de Freitas, MD) 5. Universidade Federal do Ceará (Renan Montenegro Junior, MD)
Data Collection Procedures	Retrospective, non-interventional, observational, closed cohort, longitudinal study design based on medical charts of metreleptin-naïve patients diagnosed with GL or PL prior to January 1, 2015. De-identified data for this study were collected from each site (e.g., investigators, research nurses, research assistants) into a single electronic database.
Data Analysis	All analyses were conducted for the entire sample, and by type of lipodystrophy (i.e., GL and PL) separately. **Objective 1**: Continuous variables were described in terms of means, standard deviations, and medians. Categorical were reported through frequencies and proportions. Standard errors for count variables were reported. **Objective 2**: Time to first organ damage and time to progression were analyzed through Kaplan-Meier analyses. Progression in the number of damaged organs (i.e., from 0 to 1, 1 to 2, 2 to 3, and 3 to 4) was also described using Kaplan-Meier analyses. **Objective 3**: Overall survival was described from the appearance of first evidence of GL or PL (i.e., first of appearance of symptoms or diagnosis) and from birth. Time to death was described using Kaplan-Meier analyses.
Privacy and Ethics	All patient data were de-identified prior to analysis. This study is non-interventional, no specific drug was investigated, and no prospective data were collected. This study was approved by local institutional review boards across all sites.
Note about PL patients: Not all included PL patients meet the criteria of low leptin levels, elevated A1c, and/or elevated triglycerides which have been proposed for the metreleptin EMA labelling. **Note about participating sites:** As of February 2018, data collection for Brazil was not yet complete. Data for the 178 patients from sites in the US and Turkey are shown.	

Table 9: Baseline characteristics for the GL/PL study, taken from an unpublished report included in the company's response to clarification questions

Characteristic	GL (N = 56)	PL (N = 122)	All (N=178)
Female, n (%)	33 (58.9)	86 (70.5)	119 (66.9)
Race, n (%)			
Caucasian	11 (19.6)	63 (51.6)	74 (41.6)
Black	11 (19.6)	2 (1.6)	13 (7.3)
Asian/Native American/Hispanic/Other[$]	0 (0)/0 (0)/1 (1.8)/33 (58.9)	0 (0)/0 (0)/5 (4.1)/53 (43.4)	0 (0)/0 (0)/6 (3.4)/86 (46.3)
Age at diagnosis, years, median (IQR)	11 (4, 21)	34 (24, 48)	29 (13, 43)
<18 years (%)	37 (66.1)	20 (16.4)	57 (32.0)
≥18 years (%)	19 (33.9)	102 (83.6)	121 (68.0)

Characteristic	GL (N = 56)	PL (N = 122)	All (N=178)
LD type, n (%)			
Acquired	5 (8.9)	26 (21.3)	31 (17.4)
Congenital/Familial	49 (87.5)	96 (78.7)	145 (81.5)
Fasting leptin, ng/ml			
n (%)	1 (5.9)	14 (25.9)	15 (21.1)
mean (SD)	1.2 (0)	8.8 (7.7)	8.3(7.7)
BMI, kg/m^2, median (range)	NR	NR	NR
HbA_{1c}, %			
n (%)	6 (35.3)	40 (74.1)	46 (64.8)
Mean (SD)	8.1 (3.4)	7.4 (2.0)	7.5 (2.2)
≥6.5, n (%), n (%)	3 (50.0)	22 (55.0)	25 (54.3)
≥8.0, n (%), n (%)	3 (50.0)	15 (37.5)	18 (39.1)
Fasting plasma glucose, mmol/L			
n (%)	12 (70.6)	33 (61.1)	45 (63.4)
mean (SD)	150.0 (116.6)	163.7 (71.5)	160.0 (84.6)
Fasting triglycerides*, mmol/L			
n (%)	13 (76.5)	46 (85.2)	59 (83.1)
Mean (SD)	5.4 (3.7)	5.1 (6.9)	5.1 (6.3)
≥2.26 mmol/L, n (%)	10 (76.9)	25 (54.3)	35 (59.3)
≥5.65 mmol/L, n (%)	6 (46.2)	10 (21.7)	16 (27.1)
ALT			
n (%)	16 (94.1)	49 (90.7)	65 (91.5)
ALT, >ULN, n (%)	5 (31.3)	13 (26.5)	18 (27.7)
AST			
n (%)	16 (94.1)	47 (87.0)	63 (88.7)
AST, >ULN, n (%)	3 (18.8)	5 (10.6)	8 (12.7)
Anti-diabetic medications at baseline, n (%)	NR	NR	NR
Lipid-lowering medications at baseline, n (%)	NR	NR	NR
Liver damage	15 (26.8)	27 (22.1)	42 (23.6)
Kidney damage	4 (7.1)	14 (11.5)	18 (10.1)
Heart damage	8 (14.3)	10 (8.2)	18 (10.1)
Pancreatitis	2 (3.6)	8 (6.6)	10 (5.6)

*Fasting triglycerides converted from reported units (mg/dL) to mmol/L
[$]Of those participants who's ethnicity was classified as 'other', 80/86 were Turkish
Liver damage includes chronic hepatitis, mild to severe fibrosis, cirrhosis, hepatic steatosis, hepatomegaly, transplant and other types of liver disease (n=5)
Kidney damage includes albuminuria, nephropathy, proteinuria, kidney failure requiring dialysis or transplant, transplant and other kidney disease (n=7)
Heart damage includes angina, atherosclerosis, atrial fibrillation, cardiac arrhythmia, cardiomyopathy, heart failure, ischemia, left ventricular hypertrophy, myocardial infarction, transplant and other heart abnormalities (n=10)

4.2.2 Details of relevant studies not included in the submission

As noted in section 4.2.1, nine studies[48-56] which met the pre-specified inclusion criteria[1] and were consistent with the NICE scope[27] were inappropriately excluded from the submission. In addition, details of the methods and results of the two main studies (the GL/PL natural history study and the NIH follow-up study) used to inform the cost effectiveness analysis were not included in the submission; study reports[40, 46] were provided in the company's response to clarification questions and, as far as possible, we have included information from these documents in our report.

The company's response to clarification questions acknowledged that: 'One of the primary objectives of the NIH Follow-Up study was to build on the NIH pivotal trial and extend it in two ways: a) increase the patient sample size (from 107 to 112), and b) expand the outcomes evaluated from biomarkers such as HbA_{1c} and triglycerides to more direct measures of clinical burden for patients including hyperphagia, organ abnormalities, physical appearance, ability to perform work/school, mortality, etc.'[39] No justification was provided for not reporting results for patient perceived outcomes from the NIH follow-up study in the CS, beyond a statement that: 'The NIH Follow-Up study included many of these clinical outcomes and they are incorporated into the CE model.'[39]

4.2.3 Summary and critique of company's analysis of validity assessment

The company provided an appraisal of the validity of the two metreleptin intervention studies included in the CS,[37, 38] using seven criteria based on the 12 CASP questions for cohort studies (see Section 4.1.4):

- Was the cohort recruited in an acceptable way?
- Was the exposure accurately measured to minimise bias?
- Was the outcome accurately measured to minimise bias?
- Have the authors identified all important confounding factors?
- Have the authors taken account of the confounding factors in the design and/or analysis?
- Was the follow-up of patients complete?
- How precise (for example, in terms of confidence interval and p values) are the results?

The validity assessment performed by the company (Section 9.5.1, CS pages 87-90, and corrected in the response to clarification questions) is reproduced in Tables 10 and 11 below.

Table 10: Critical appraisal of study NIH 991265/20010769

Study name: NIH 991265/20010769		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	The patient population was representative of a defined population. The patients had low leptin levels (<12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years) and at least 1 metabolic abnormality out of diabetes mellitus; fasting insulin concentration >30 μU/mL, and/or fasting triglyceride concentration >2.26 mmol/L or postprandially elevated triglycerides >5.65 mmol/L when fasting was clinically not indicated (e.g., in infants); these are the hallmarks of this syndrome, i.e., insulin resistance with diabetes mellitus and hypertriglyceridemia. Patients were recruited from different regions across the world.
Was the exposure accurately measured to minimise bias?	Yes	Exposure was clearly defined and accurately measured. The measurement of exposure was objective i.e. dose and duration, including average (mean [SD], median and range) for daily dose (mg/day), and weighted average dose (mg/kg).
Was the outcome accurately measured to minimise bias?	Yes	The study's efficacy endpoints were objective measurements, including the co-primary endpoints of HbA_{1c} and triglycerides. These measurements were primarily obtained at a single laboratory and thus treatment effects could be appropriately evaluated. The efficacy endpoints were clinically relevant to the patient and the progression of disease.
Have the authors identified all important confounding factors?	Yes	Potential confounding factors included: concomitant medication use, sex, race, age, weight, height, body weight category, BMI, region, LD subtype (CGL, AGL, FPL, APL), gene mutation (LMNA, PPARg, Seipin, AGPAT-2, ZMPSTE24, Other, and not applicable), baseline laboratory values.

Study name: NIH 991265/20010769		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	In addition to the FAS, efficacy was analysed on the CFAS, which included all patients in the FAS who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid lowering therapies), prior to Month 12. Data for all anti-diabetic or lipid lowering therapies, including type, dose, regimen, and route of administration, underwent medical review and patients who had these types of medications added or doses increased that may have had an impact on the efficacy endpoints were excluded from the CFAS. Patients were excluded separately based on the type of medication that was added or increased, e.g., patients with potentially confounding anti-diabetes medications were excluded from the analyses of HbA_{1c} and those with potentially confounding lipid-lowering therapies were excluded from analyses of triglycerides. In general, the results for the efficacy analyses were consistent for the FAS and the CFAS. In addition, subgroup analyses were conducted based on a number of baseline characteristics to show whether treatment effects were observed consistently across relevant populations. including: LD subtype (AGL, CGL, FPL, and APL); age (age categories <6, ≥6 to <12, ≥12 to <18, < 18, and ≥18 years old); region (US, EU, EU and Eastern Mediterranean, and Other); presence of metabolic abnormalities at baseline (HbA_{1c} [<6.5 and ≥6.5%], ≥7%, ≥8% and fasting triglycerides [<2.26 mmol/L and ≥2.26 mmol/L / <200 and ≥200 mg/dL, ≥5.65 mmol/L / ≥500 mg/dL; and between ≥2.26 and ≤5.65 mmol/L / ≥200 and ≤500 mg/dL]); concomitant insulin, anti-diabetic medications and lipid-lowering medications at baseline; baseline leptin levels (<12 ng/mL / ≥12 ng/mL, primary efficacy analysis only) (see Section 9.6.1.5)
Was the follow-up of patients complete?	Yes	Only one patient was lost to follow-up (see Section 9.4.7)

Study name: NIH 991265/20010769		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
How precise (for example, in terms of confidence interval and p values) are the results?	Yes, the precision of the results is reasonable	The following results with 95% CIs were reported were reported: GL patients: mean change from baseline to Month 12/LOCF for HbA_{1c} was -2.2% (95% CI: -2.7, -1.6) and the mean percent change in triglycerides was -32.1% (-51.0, -13.2) PL subgroup[a] patients (excluding outlier patient): mean change from baseline to Month 12/LOCF for HbA_{1c} was -0.9% (95% CI: -1.4, -0.4) and the mean percent change in triglycerides was -37.4% (-57.2, -8.6). The majority of patients in both the GL group and the PL subgroup achieved meaningful reductions in both HbA_{1c} and triglycerides.
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		
Abbreviations: AGL = acquired generalised lipodystrophy; APL = acquired partial lipodystrophy; BMI = body mass index; CFAS = Controlled Concomitant Medication Full Analysis Set; CGL = congenital generalised lipodystrophy; CI = confidence interval; EU = European Union; FAS = full analysis set; FPL = familial partial lipodystrophy; GL = generalised lipodystrophy; HbA_{1c} = glycated haemoglobin; LD = lipodystrophy; LOCF = last observation carried forward; PL = partial lipodystrophy; SD = standard deviation; US = United States		

Table 11: Critical appraisal of study FH101

Study name: FHA101		
Study question	Response yes/no/not clear/N/A)	How is the question addressed in the study?
Was the cohort recruited in an acceptable way?	Yes	The patient population was representative of a defined population. Patients had to have been diagnosed with at least 1 of the following 2 metabolic disorders: diabetes mellitus and/or hypertriglyceridemia as defined by fasting triglyceride concentrations >2.26 mmol/L (>200 mg/dL), which are the hallmark of this syndrome
Was the exposure accurately measured to minimise bias?	Yes	Exposure was clearly defined and accurately measured. The measurement of exposure was objective i.e. dose and duration, including average (mean [SD], median and range) for daily dose (mg/day), weighted average dose (mg/kg).
Was the outcome accurately measured to minimise bias?	Yes	The study's efficacy endpoints were objective measurements, including the co-primary endpoints of HbA_{1c} and triglycerides. These measurements were primarily obtained at a single laboratory and thus treatment effects could be appropriately evaluated. The efficacy endpoints were clinically relevant to the patient and the progression of disease.
Have the authors identified all important confounding factors?	Yes	Potential confounding factors included: concomitant medication use, sex, race, age, weight, height, body weight category, BMI, region (US, EU, EU and Eastern Mediterranean, other), LD subtype (CGL, AGL, FPL, APL), gene mutation (LMNA, PPARg, Seipin, AGPAT-2, ZMPSTE24, Other, and Not Applicable), baseline laboratory values
Have the authors taken account of the confounding factors in the design and/or analysis?	Partially	As in study NIH 991265/20010769 efficacy was analysed on the FAS and the CFAS, which included all patients in the FAS who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid lowering therapies), prior to Month 12. In general, the results for the efficacy analyses were consistent for the FAS and the CFAS.
Was the follow-up of patients complete?	Yes	Only two patients were lost to follow-up (see Section **Error! eference source not found.**)
How precise (for example, in terms of confidence interval and p values) are the results?	Due to the small sample sizes, the 95% CIs were wide	The following results with 95% CIs were reported were reported: GL patients: mean change from baseline to Month 12/LOCF for HbA_{1c} was -1.2 % (95% CI: -4.3, 2.0) and the mean percent change in triglycerides was -26.9% (-124.1, 70.4) PL subgroup patients (excluding outlier patient): mean change from baseline to Month 12/LOCF for HbA_{1c} was -0.9% (95% CI: -1.4, -0.4) and the mean percent change in triglycerides was -8.5% (-36.4, 19.5).
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

Abbreviations: AGL, acquired generalised lipodystrophy; APL = acquired partial lipodystrophy; BMI = body mass index; CFAS = Controlled Concomitant Medication Full Analysis Set; CGL = congenital generalised lipodystrophy; CI = confidence interval; EU = European Union; FAS = full analysis set; FPL = familial partial lipodystrophy; GL = generalised lipodystrophy; HbA_{1c} = glycated haemoglobin; LD = lipodystrophy; LOCF = last observation carried forward; PL = partial lipodystrophy; SD = standard deviation; US = United States

The ERG agrees with the content of the critical appraisals provided, but does not consider this to be an adequate approach to assessing risk of bias in a cohort study (see Section 4.1.4).

No critical appraisal or risk of bias assessment was provided for the GL/PL natural history study.

4.2.4 Summary and critique of results

For the evaluation of clinical effectiveness of any treatment, a comparison between treated and untreated patients, who are similar with respect to characteristics other than treatment, is needed. Clinical or 'patient-perceived' outcomes, such as organ damage or hyperphagia, are more relevant than biochemical markers of 'surrogate outcome measures', such as triglyceride levels or HbA_{1c}. The CS (pages 90-95 and 103-104) focuses on change from baseline, in triglyceride levels or HbA_{1c}, in metreleptin treated patients. These results, along with any results for clinical outcomes included in the CS (pages 98-100) are reproduced and critiqued below.

We have added further results for clinical outcomes, which were not included in the CS, including results from the NIH follow-up study and the GL/PL natural history study, for which no results were reported in the CS.

Efficacy

Change in HbA_{1c} and triglycerides

The single arm metreleptin treatment study, NIH 991265/20010769, found statistically significant reductions in both HbA_{1c} and triglyceride levels in both GL and PL.[37] The mean (SD) actual change in % HbA_{1c}, from baseline to month 12 of treatment, LOCF, was -2.2 (2.15) for GL patients, -0.9 (1.23) for the PL subgroup and -0.6 (1.22) for all PL patients. The corresponding values, for % change in triglyceride levels, were -32.1 (71.28) for GL patients, -37.4 (30.81) for the PL subgroup and -20.8 (47.93) for all PL patients. Full results for markers of glycaemic control and lipid metabolism are provided in Table 12 below, reproduced from the CS (CS, Table C22, pages 90-92).[1]

Additional data were presented in the CS (pages 96-97) to support the persistence of these effects to 36 months. The CS also includes some subgroup data for changes in percentage HbA_{1c} and triglycerides. In general, greater mean decreases from baseline to the primary time point of Month 12/LOCF were observed amongst patients who had higher baseline percentage HbA_{1c} and triglyceride levels. Similarly, patients with the acquired forms of LD generally achieved larger mean decreases from baseline compared with patients who had the congenital/familial form. Subgroup data for markers of glycaemic control and lipid metabolism are provided in Table 13 below, reproduced from the CS (CS, Table C23, pages 101-102).[1]

ERG comment: Subgroup data were not provided for the overall PL population.

The smaller, single arm metreleptin treatment study, FH101, reported decreases in percentage HbA_{1c} and triglyceride levels, from baseline to month 12 of treatment, in all patient groups. However, these decreases were not statistically significant. Full results for markers of

glycaemic control and lipid metabolism are provided in Table 14 below, reproduced from the CS (CS, Table C24, pages 103-105).[1]

ERG comment: One study, which met the pre-specified inclusion criteria but was excluded from the CS (see section 4.2.1,[50] assessed the effects of leptin therapy in 24 female patients with Dunnigan variety FPL and moderate or severe hypoleptinemia and found no significant change from baseline to six months in fasting glucose, insulin, glucose tolerance, or HbA_{1c} levels.

The GL/PL natural history study[40] did not report any information about changes in markers of glycaemic control or lipid metabolism over time.

Table 12: Glycaemic control and lipid metabolism results from NIH 991265/20010769 study

Study name		NIH 991265/20010769		
Size of study groups	**Treatment**	GL = 62 PL subgroup[a] = 30 PL overall = 40		
Study duration	**Time unit**	12 months		
Type of analysis	**Intention-to - treat/per protocol**	FAS: all patients who received at least 1 dose of study drug and who had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit		
Co-primary endpoint: Change from baseline in HbA_{1c} (%) using LOCF (FAS population, excluding outlier patient[b])				
		GL N = 62	PL subgroup N = 29[a.b]	PL overall N = 39[b]
Baseline value	**n**	62	29	39
	Mean (SD)	8.6 (2.33)	8.8 (1.91)	8.0 (2.18)
Month 12 value, LOCF	**n**	59	27	36
	Mean (SD)	6.4 (1.68)	8.0 (1.83)	7.5 (1.84)
Effect size: actual change from baseline	**n**	59	27	36
	Mean (SD)	-2.2 (2.15)	-0.9 (1.23)	-0.6 (1.22)
	95% CI	-2.7, -1.6	-1.4, -0.4	-1.0, -0.2
Statistical test	**Type**	P values computed using paired t-tests		
	p value	<0.001	<0.001	0.005
Co-primary endpoint: Change from baseline in triglycerides (mmol/L) using LOCF (FAS population, excluding outlier patient[b])				
		GL N = 62	PL subgroup N = 29[a, b]	PL overall N = 39[b]
Baseline value	**n**			
	Mean (SD)	14.7 (25.66)	15.7 (26.42)	12.5 (23.35)
Month 12 value, LOCF	**n**			
	Mean (SD)	4.5 (6.10)	6.0 (8.41)	5.4 (7.37)
Effect size: percent change from baseline	**n**	57	27	36
	Mean (SD)	-32.1 (71.28)	-37.4 (30.81)	-20.8 (47.93)
	95% CI	-51.0, -13.2	-57.2, -8.6	-51.0, -13.2

Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.001	<0.001	0.013
Key secondary endpoint: Actual and percent change from baseline in fasting plasma glucose levels at Month 12 (mmol/L) using LOCF (FAS population)				
		GL N = 62	PL subgroup N = 30[a]	PL overall N = 40
Baseline value	**n**			
	Mean (SD)	10.2 (5.05)	10.0 (4.36)	8.8 (4.39)
Month 12 value, LOCF	**n**	59	28	37
	Mean (SD)	7.0 (3.40)	8.1 (3.55)	7.5 (3.28)
Effect size: actual change from baseline	**n**	59	28	37
	Mean (SD)	-3.0 (4.72)	-1.8 (2.83)	-1.2 (2.69)
	95% CI	-4.2, -1.7	-2.9, -0.7	-2.1, -0.3
Statistical test	**Type**	P values computed using paired t-tests		
	p value	<0.001	0.003	0.012
Effect size: percent change from baseline	**n**	59	28	37
	Mean (SD)	-19.7 (37.21)	-13.2 (28.99)	-6.1 (29.59)
	95% CI	-29.4, -10.0	-24.4, -1.9	-16.0, 3.8
Statistical test	**Type**	P values computed using paired t-tests		
	p value	<0.001	0.023	0.219
Key secondary endpoint: Responder analysis: patients who met target reductions in HbA_{1c} or triglycerides at Month 12/LOCF (FAS population)				
		GL N = 62	PL subgroup N = 30[a]	PL overall N = 40
≥1% actual decrease in HbA_{1c} or ≥30% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	47/59 (79.7)	19/28 (67.9)	19/37 (51.4)
	95% CI[c]	(67.2, 89.0)	(47.7, 84.1)	(34.4, 68.1)
≥1.5% actual decrease in HbA_{1c} or ≥35% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	44/59 (74.6)	14/28 (50.0)	14/37 (37.8)
	95% CI[c]	61.6, 85.0	30.7, 69.4	22.5, 55.2
≥2% actual decrease in HbA_{1c} or ≥40% decrease in triglycerides				

Month 12 value, LOCF	**n/N1 (%)**	39/59 (66.1)	12/28 (42.9)	12/37 (32.4)
	95% CI[c]	52.6, 77.9	24.5, 62.8	18.0, 49.8
Other secondary endpoints: Change from baseline to Month 12/LOCF in fasting lipids (FAS population)				
		GL N = 62	PL subgroup N = 30[a]	PL overall N = 40
Total cholesterol (mmol/L)				
Baseline	**n**	62	30	40
	Mean (SD)	5.9 (3.66)	6.4 (2.80)	5.9 (2.62)
Actual change from **baseline**	**n**	41	21	30
	Mean (SD)	-2.3 (2.91)	-0.9 (1.52)	-0.6 (1.45)
LDL-C (mmol/L)				
Baseline	**n**	37	17	24
	Mean (SD)	2.6 (1.35)	2.8 (1.02)	2.6 (1.01)
Actual change from **baseline**	**n**	22	12	18
	Mean (SD)	-0.9 (1.29)	-0.3 (0.66)	-0.1 (0.62)
HDL-C (mmol/L)				
Baseline	**n**	56	25	35
	Mean (SD)	0.7 (0.25)	0.8 (0.23)	0.8 (0.21)
Actual Change from **BL**	**n**	35	17	26
	Mean (SD)	-0.0 (0.24)	0.0 (0.14)	0.0 (0.14)

Abbreviations: CI, confidence interval; FAS, full analysis set; GL, generalised lipodystrophy; HbA_{1c}, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LOCF, last observation carried forward; PL, partial lipodystrophy; SD, standard deviation

[a] PL subgroup = patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] Excluding results for Patient 901-080 who had an outlier value for percent increase from baseline in triglycerides of >1000% at Month 12/LOCF. The patient was terminated from treatment by the Investigator for noncompliance with dosing

Table 13: Glycaemic control and lipid metabolism subgroup results from NIH 991265/20010769 study

	GL				PL subgroup[a,b]			
	HbA_{1c}		Triglycerides		HbA_{1c}		Triglycerides	
	N	**Mean (SD) actual Δ to Month 12**	N	**Mean (SD) percent Δ to Month 12**	N	**Mean (SD) actual Δ to Month 12**	N	**Mean (SD) percent Δ to Month 12**
Baseline HbA_{1c} (%):								
<6.5	14	-0.1 (0.35)	14	-4.1 (55.58)	2	0.1 (0.64)	2	-40.8 (27.29)
≥6.5	45	-2.8 (2.08)	43	-41.2 (73.97)	25	-1.0 (1.24)	25	-37.1 (31.57)
≥7	45	-2.8 (2.08)	43	-41.2 (73.97)	23	-1.1 (1.28)	23	-37.2 (32.95)
≥8	39	-3.0 (2.13)	37	-38.6 (78.36)	18	-1.3 (1.33)	18	-43.6 (33.60)
Baseline triglycerides (mmol/L):								
<2.26	13	-1.6 (1.71)	13	6.7 (44.20)	3	-0.9 (0.36)	3	-20.7 (28.33)
≥2.26	45	-2.3 (2.28)	45	-42.5 (73.87)	24	-0.9 (1.31)	24	-39.5 (31.03)
≥5.65	24	-3.3 (2.56)	24	-72.0 (25.09)	15	-1.0 (1.62)	15	-53.7 (25.21)
LD type								
Congenital/ Familial	40	-1.8 (1.92)	39	-22.2 (80.54)	23	-0.7 (0.88)	23	-37.4 (26.64)
Acquired	19	-2.9 (2.47)	18	-53.5 (39.09)	4	-2.0 (2.42)	4	-37.0 (54.98)
Age (years)								
< 6	5	0.2 (0.60)	5	-10.5 (58.18)	0	NA	0	NA
≥6 to <12	11	-1.1 (1.51)	11	-14.1 (49.74)	0	NA	0	NA
≥12 to <18	24	-2.6 (1.89)	23	-42.9 (45.55)	5	-0.6 (1.24)	5	-50.6 (33.62)
≥18	19	-2.8 (2.46)	18	-35.3 (106.23)	22	-1.0 (1.25)	22	-34.4 (30.15)
Region[c]								
US	34	-1.9 (2.02)	34	-23.2 (85.87)	20	-1.0 (1.32)	20	-41.8 (27.97)
EU and EM	11	-2.6 (1.96)	11	-52.1 (41.84)	2	-0.7 (0.28)	2	13.3 (38.20)
EU	7	-1.5 (1.45)	7	-38.7 (48.04)	1	-0.5 (NA)	1	40.3 (NA)
Other	12	-2.6 (2.81)	11	-39.5 (39.99)	5	-0.8 (1.23)	5	-39.8 (26.45)

Abbreviations: **Δ,** change; EU, European Union, EM, Eastern Mediterranean; FAS, Full Analysis Set; GL, generalised lipodystrophy; HbA_{1c}, glycated haemoglobin; LOCF, last observation carried forward; NA, non-applicable; PL, partial lipodystrophy; SD, standard deviation; US, United States

[a] PL subgroup = patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] Excluding results for Patient 901-080 who had an outlier value for percent increase from baseline in triglycerides of >1000% at Month 12/LOCF. The patient was terminated from treatment by the Investigator for noncompliance with dosing (Study NIH 991265/20010769, Listing 16.2.1.1)

[c] EU includes Belgium, UK, Germany, Italy, Lithuania, and Spain; EM includes Turkey, Albania, Israel, and Serbia; Other includes Argentina, Canada, India, Madagascar, Pakistan, Peru, and Saudi Arabia

Table 14: Glycaemic control and lipid metabolism, results from FH101 study

Study name		FHA101		
Size of study groups	**Treatment**	GL = 9 PL subgroup[a] = 7 PL overall = 29		
Study duration	**Time unit**	12 months		
Type of analysis	**Intention-to -treat/per protocol**	FAS: all patients who received at least 1 dose of study drug and who had either primary efficacy parameter of interest measured at baseline and at least one post-baseline visit		
Co-primary endpoint: Change from baseline in HbA_{1c} (%) using LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
Baseline value	**n**	9	7	29
	Mean (SD)	7.7 (1.99)	7.8 (1.71)	8.1 (1.77)
Month 12 value, LOCF	**n**	5	7	26
	Mean (SD)	6.2 (1.96)	7.0 (0.76)	7.8 (1.76)
Effect size: actual change from baseline	**n**	5	7	26
	Mean (SD)	-1.2 (2.53)	-0.8 (1.85)	-0.4 (1.49)
	95% CI	-4.3, 2.0	-2.5, 0.9	-1.0, 0.2
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.360	0.289	0.210
Co-primary endpoint: Change from baseline in triglycerides (mmol/L) using LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
Baseline value	**n**	8	7	29
	Mean (SD)	19.9 (40.90)	4.0 (4.54)	8.5 (12.37)
Month 12 value, LOCF	**n**	6	7	26
	Mean (SD)	7.6 (11.10)	3.6 (3.57)	6.4 (10.06)
Effect size: percent change from baseline	**n**	5	7	26
	Mean (SD)	-26.9 (78.32)	-8.5 (30.22)	8.7 (93.39)
	95% CI	-124.1, 70.4	-36.4, 19.5	-29.1, 46.4

Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.486	0.485	0.640
Key secondary endpoint: Actual and percent change from baseline in fasting plasma glucose levels at Month 12 (mmol/L) using LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
Baseline value	**n**	9	7	29
	Mean (SD)	11.4 (6.03)	8.0 (2.83)	8.5 (3.45)
Month 12 value, LOCF	**n**	6	7	27
	Mean (SD)	10.2 (7.58)	6.9 (2.16)	8.3 (2.99)
Effect size: actual change from BL	**n**	6	7	27
	Mean (SD)	-1.5 (9.90)	-1.1 (2.95)	-0.2 (4.14)
	95% CI	-11.9, 8.8	-3.8, 1.6	-1.8, 1.5
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.719	0.358	0.838
Effect size: percent change from baseline	**n**	6	7	27
	Mean (SD)	-7.3 (53.71)	-9.0 (26.45)	13.9 (69.14)
	95% CI	-63.6, 49.1	-33.4, 15.5	-13.4, 41.3
Statistical test	**Type**	P values computed using paired t-tests		
	p value	0.754	0.403	0.304
Key secondary endpoint: Responder analysis: patients who met target reductions in HbA_{1c} or triglycerides at Month 12/LOCF (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
≥1% actual decrease in HbA_{1c} or ≥30% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	3/6 (50.0)	2/7 (28.6)	9/26 (34.6)
	95% CI[b]	11.8, 88.2	3.7, 71.0	17.2, 55.7
≥1.5% actual decrease in HbA_{1c} or ≥35% decrease in triglycerides				
Month 12 value, LOCF	**n/N1 (%)**	3/6 (50.0)	2/7 (28.6)	9/26 (34.6)
	95% CI[b]	11.8, 88.2	3.7, 71.0	17.2, 55.7
≥2% actual decrease in HbA_{1c} or ≥40% decrease in triglycerides				

Month 12 value, LOCF	**n/N1 (%)**	3/6 (50.0)	1/7 (14.3)	7/26 (26.9)
	95% CI[b]	11.8, 88.2	0.4, 57.9	11.6, 47.8
	Mean (SD)	-104.1 (74.18)	-0.3 (7.21)	-3.6 (24.81)

Abbreviations: CI, confidence interval; FAS, full analysis set; GL, generalised lipodystrophy; HbA_{1c}, glycated haemoglobin; LOCF, last observation carried forward; PL, partial lipodystrophy; SD, standard deviation

[a] PL subgroup = patients with baseline leptin <12 ng/mL and HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

[b] 95% CI based on the 2-sided exact binomial proportions

Persistence of change in HbA_{1c} and triglycerides over time

The CS[37] reports some information about longer term (up to 36 months) changes in HbA_{1c} and triglycerides in patients on metreleptin treatment. Least-squares mean (LS mean) changes from baseline in HbA_{1c} in the GL group based on a mixed model repeated measures (MMRM) analysis were -2.3%, -2.1% and -1.5% at Months 12, 24 and 36, respectively.[1, 37] The overall MMRM analysis showed a statistically significant decrease from baseline for GL patients with an LS mean change of -1.4% ($p<0.001$). Results were similar in the PL subgroup with LS mean changes in HbA_{1c} of -0.9%, -1.3%, and -1.0% at Months 12, 24, and 36 and an overall LS mean change of -0.6% ($p<0.001$).[1, 37]

In the GL group, LS mean percent changes from baseline in triglycerides were -48.3%, -22.6% and -40.6% at Months 12, 24, and 36, respectively; based on the overall MMRM analysis, the LS mean change in triglycerides was -22.4% ($p<0.001$). For the PL subgroup (excluding data from the 'outlier' patient described previously), LS mean percent changes in triglycerides were -36.2%, -31.7%, and -13.7% at Months 12, 24 and 36, respectively, with an overall LS mean change of -18.6% ($p=0.004$).[1, 37]

ERG comment: Data for the overall PL population (not included in the CS) indicated no statistically significant change in triglyceride levels over time. The LS mean (SEM) percentage change values were as follows: month 12 = -16.7 (8.62), p = 0.054; month 24 = -9.4 (16.41), p = 0.566; month 36 =4.4 (17.53), p = 0/801; overall MMRM = -8.3 (5.46), p=0.131.[37]

Liver function (hepatic enzymes), liver pathology

Data from the NIH 991265/20010769 study,[1, 37] suggest that metreleptin treatment may be associated reductions in hepatic enzymes. In the 41 GL patients with hepatic data available, the mean (SD) changes, in ALT and AST, from baseline to month 12 of treatment were -53.1 (126.56) U/L and -23.8 (142.38) U/L, respectively. Reductions were smaller for the PL subgroup (-5.0 (11.95) and -6.0 (14.77) for ALT and AST, respectively) and for the overall PL group (-0.4 (26.95) and -5.1 (21.06) for ALT and AST, respectively. Full results for hepatic enzymes are provided in Table 15 below, reproduced from the CS (CS, Table C22, pages 90-92).[1] No assessments of statistical significance were presented.

Table 15: Hepatic enzymes results from NIH 991265/20010769 study

Change from baseline to Month 12 in liver transaminase levels (FAS Population)				
		GL N = 62	PL subgroup N = 30[a]	PL overall N = 40
ALT (U/L)				
Baseline	**n**	62	30	40
	Mean (SD)	111.9 (112.62)	39.2 (28.02)	54.8 (57.99)
Actual change from **baseline**	**n**	41	21	30
	Mean (SD)	-53.1 (126.56)	-5.0 (11.95)	-0.4 (26.95)
AST (U/L)				
Baseline	**n**	62	30	40
	Mean (SD)	75.0 (71.07)	31.9 (19.64)	38.4 (33.46)
Actual change from **baseline**	**n**	41	21	30
	Mean (SD)	-23.8 (142.38)	-6.0 (14.77)	-5.1 (21.06)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FAS, full analysis set; GL, generalised lipodystrophy; PL, partial lipodystrophy; SD, standard deviation

[a] PL subgroup = patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

ERG comment: The full CSR for the NIH 991265/20010769 study,[74] provided in response to clarification questions, also reports median (range) values for change in hepatic enzymes. These values show a wide range and are not clearly supportive of a treatment effect: The median (range) change in ALT (U/L) from baseline to 12 months of treatment was -35.0 (-368.0 to 293.5) for GL patients, -3.0 (-36.0 to12.0) for the PL subgroup and -0.5 (-56.0 to 80.0) for all PL patients; the median (range) change in AST (U/L) from baseline to 12 months of treatment was -20.5 (-331.0 to 734.0) for GL patients, -2.0 (-51.0 to 12.0) for the PL subgroup and -1.5 (-65.0 to 54.0) for all PL patients.

Similar results were reported for the smaller FH101 study (see Table 16).[1, 38]

Table 16: Hepatic enzymes results from FH101 study

Change from baseline to Month 12 in liver transaminase levels (FAS population)				
		GL N = 9	PL subgroup[a] N = 7	PL overall N = 29
ALT (U/L)				
Baseline	**n**	9	7	29
	Mean (SD)	122.1 (140.47)	35.3 (16.64)	40.7 (34.37)
Actual change from **baseline**	**n**	4	5	19
	Mean (SD)	-191.5 (167.27)	-5.1 (12.94)	-7.4 (25.80)
AST (U/L)				
Baseline	**n**	9	7	29
	Mean (SD)	76.0 (72.52)	27.7 (8.98)	35.9 (28.44)
Actual change from **baseline**	**n**	4	5	19
	Mean (SD)	-104.1 (74.18)	-0.3 (7.21)	-3.6 (24.81)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FAS, full analysis set; GL, generalised lipodystrophy; PL, partial lipodystrophy; SD, standard deviation

[a] PL subgroup = patients with baseline leptin <12 ng/mL and HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

The CS states that a total of 21 patients with GL and eight patients in the PL subgroup had liver volume assessed at baseline and at least one post-baseline assessment,[1, 37] 20 of 21 patients with GL and six of the eight patients in the PL subgroup had hepatomegaly (liver volume >2000 mL). Reductions in liver volume were observed at all post-baseline assessments in 15 (71%) of the 21 patients with GL who could be assessed for changes from baseline and an additional four patients had reductions at all assessments on or after Month 12. Reductions in liver volume for these 19 patients ranged from 7% to 71%, with most patients (12 of 19) having reductions of ≥30%. Among the eight patients in the PL subgroup, four (50%) had reductions observed at all post-baseline assessments and an additional patient had reductions at all assessments on or after Month 12. Reductions in liver volume for these five patients ranged from 8% to 51%. Among paediatric patients, reductions from baseline were observed at all assessments in 10 (77%) of 13 patients with data available, all with GL; the remaining three patients had reductions at all assessments after Month 12. Reductions ranged from 7% to 64% with most of these paediatric patients (eight of 13) having reductions ≥30%.[1, 37]

ERG comment: The median (range) of observed change in liver volume (mL) from baseline to month 12 of treatment, taken full CSR for the NIH 991265/20010769 study[74] provided in response to clarification questions, was -34.8 (-53.9 to -10.0) for GL patients (n=12), -15.8 (-21.2 to 4.4 for the PL subgroup (n=7) and -16.7 (-21.2 to 4.4) for all PL patients (n=8).

Results of paired liver biopsies from 27 patients in Study NIH 991265/20010769 were reported in the publication by Safar-Zadeh et al.2013[24] Of these 27 patients, 86% had borderline or definite NASH at baseline and 33% had NASH after leptin replacement for 25.8 ± 3.7 months

(p = 0.0002).[24] Significant improvements were observed in steatosis grade and ballooning injury scores with a reduction in the NAFLD activity score during long-term treatment with metreleptin in patients with NASH.[1, 24, 69] Patients with liver fibrosis at baseline remained stable on metreleptin.[1, 24, 69]

ERG comment: The CS lacks long-term data about the effects of metreleptin on the development and progression of liver disease. The ongoing studies section of the CS (CS, page 27) states that: 'The NIH Follow-Up study has allowed for consideration of longer history and follow-up across a range of outcomes not fully studied in the clinical trial. While the retrospective and observational nature of this single-arm study is acknowledged, a wealth of information about these patients' experiences with LD both before and after initiation with metreleptin has been reported, including outcomes such as hyperphagia, female reproductive dysfunction, damage to key organ systems, and death.'[1] However, no results from this study are reported in the clinical effectiveness sections of the CS; a study report was provided in response to clarification questions.[46] This report defined an improvement in liver abnormality as at least a 20% reduction in AST/ALT at one year post-metreleptin initiation, in patients who had evidence of pre-treatment liver abnormalities, and no additional emergent liver abnormalities during that year; liver abnormalities included hepatomegaly, any form of fatty liver or steatosis, fibrosis, cirrhosis, and hepatitis (see section 4.2.1, Table 6) and only 56/105 (53%) of patients who were classified as having pre-treatment liver abnormalities also had elevated hepatic enzymes. Of the 63 GL patients with evidence of pre-metreleptin liver abnormalities, 32 (51%) were classified as having post-metreleptin improvement, compared to 6/42 (14%) for PL patients; no data were reported for the PL subgroup.[46] It should be noted that, whilst these data appear to be evidence that metreleptin treatment is associated with improvements in liver function, a decrease in AST/ALT levels, set at an apparently arbitrary threshold of 20%, is a surrogate outcome measure and is unlikely to be an adequate indicator of long term clinical outcomes. Of the five GL patients who had no evidence of liver abnormalities before metreleptin treatment, two (40%) had emergent liver abnormalities after metreleptin initiation; there were no emergent liver abnormalities in the PL population.[46] No indication of mean/median length of follow-up was provided.

ERG comment: The CS did not report any comparator results for development and progression of liver disease (from the GL/PL natural history study); a study report was provided in response to clarification questions.[40] This report included information on the number of patients with liver damage (including chronic hepatitis, mild to severe fibrosis, cirrhosis, hepatic steatosis, hepatomegaly, and transplant) at baseline; the baseline period was defined as birth to first known date of GL or PL diagnosis (see Section 4.2.1, Table 6) and the number of patients with liver abnormalities over the whole observation period, including baseline and follow-up period (time from first known date of GL or PL diagnosis to date of chart abstraction, death or loss to follow-up). The mean follow-up period for GL patients was 8.8 years and the mean follow-up period for PL patients was 5.7 years.[40] Over the whole observation period, 50/56 (89.3%) of GL patients and 79/122 (64.8%) of PL patients were found to have liver damage.[40] Using the reported data for the baseline period and the whole observation period, it is possible to calculate the proportion of patients who did not have liver damage at baseline,

but developed liver damage during the follow-up period (after GL/PL diagnosis). Of the 41 GL patients who did not have liver damage at baseline 35 (85.4%) developed liver damage during follow-up and 52/95 (54.7%) of PL patients who did not have liver damage at baseline developed damage during follow-up.

Other organ damage (heart and kidneys)
The clinical effectiveness section of the CS does not include any evidence about the effects of metreleptin treatment on the development or progression of heart or kidney damage.[1]

ERG comment: In the study report for the NIH follow-up study[46] a patient's heart abnormality was considered to have improved at one year post-metreleptin initiation if they were classified as pre-hypertensive (systolic <140 or ≥120 or diastolic <90 or ≥80) at baseline and normal (systolic <120 and diastolic <100) at one year and had no additional emergent heart conditions during that year.[46] Based on these criteria, 11/36 (31%) of GL patients and 1/14 (7%) of PL patients were classified as having experienced an improvement in their heart abnormality over one year of metreleptin treatment. However, it should be noted that heart abnormalities included hypertrophy, any dilation, any regurgitation, cardiomyopathy, and tachycardia and only 27/50 (54%) of patients with a pre-treatment heart abnormality were also classified as hypertensive or pre-hypertensive; one year changes in blood pressure alone are unlikely to provide an adequate indicator of long term clinical improvement/progression for the conditions listed. Of the 32 GL patients who had no evidence of heart abnormalities before metreleptin treatment, nine (28%) had emergent heart abnormalities after metreleptin initiation, and 6/30 (20%) of PL patients who had no evidence of heart abnormalities before treatment had emergent abnormalities after metreleptin initiation. [46] No indication of mean/median length of follow-up was provided.

Similarly, the study report for the NIH follow-up study[46] defined one year post-metreleptin improvement in kidney abnormalities as a 20% reduction in 24 hour protein excretion, where elevated 24 hour protein excretion was present at baseline, and no additional emergent kidney conditions. Based on these criteria, 19/46 (41%) of GL patients and 4/25 (16%) PL patients were classified as having experienced an improvement in their kidney abnormality over one year of metreleptin treatment. However, it should be noted that kidney abnormalities included proteinuria, enlarged kidneys, nephropathy, hydronephrosis, renal disease, nephromegaly, renal failure, renal calculus, and glomerulosclerosis and only 38/74 (51%) of patients with a pre-treatment kidney abnormality also had elevated 24 hour protein excretion; one year changes in 24 hour protein excretion alone are unlikely to provide an adequate indicator of long term clinical improvement/progression for the conditions listed. Of the 22 GL patients who had no evidence of kidney abnormalities before metreleptin treatment, eight (36%) had emergent kidney abnormalities after metreleptin initiation, and 4/19 (21%) of PL patients who had no evidence of heart abnormalities before treatment had emergent abnormalities after metreleptin initiation.[46] No indication of mean/median length of follow-up was provided.

ERG comment: The CS did not report any comparator results for development and progression of heart or kidney damage (from the GL/PL natural history study); a study report was provided in response to clarification questions.[40] This report included information on the

number of patients with kidney damage (including albuminuria, nephropathy, proteinuria, kidney failure requiring dialysis or transplant, and transplant) and heart damage (including angina, atherosclerosis, atrial fibrillation, cardiac arrhythmia, cardiomyopathy, heart failure, ischemia, left ventricular hypertrophy, myocardial infarction, and transplant) at baseline, (see Section 4.2.1, Table 6). Over the whole observation period, 28/56 (50.0%) of GL patients and 49/122 (40.2%) of PL patients were found to have kidney damage, and 22/56 (39.3%) of GL patients and 37/122 (30.3%) of PL patients were found to have heart damage.[40] Using the reported data for the baseline period and the whole observation period, it is possible to calculate the proportion of patients, who did not have organ damage at baseline, but developed kidney or heart damage during the follow-up period (after GL/PL diagnosis). Of the 52 GL patients who did not have kidney damage at baseline 24 (46.2%) developed kidney damage during follow-up and 35/108 (32.4%) of PL patients who did not have kidney damage at baseline developed damage during follow-up. Using the same approach, of the 48 GL patients who did not have heart damage at baseline 14 (29.2%) developed heart damage during follow-up and 27/112 (24.1%) of PL patients who did not have heart damage at baseline developed damage during follow-up.

Hyperphagia

The CS reports results from an additional publication of the NIH 991265/20010769 study, by Moran et al. 2004[68] This article reports food intake data for 8/14 metreleptin-treated patients LD; mean (SD) food intake in these patients decreased from 3,170 (436) kcal/day at baseline to 1,739 (162) kcal/day at four months.[68]

ERG comment: This study also reported mean (SD) food intake at 12 months (n=6) and these data indicated a subsequent increase in food intake to 2,015 (410) kcal/day (not significantly different from baseline.

The CS also reports results from a further publication, by McDuffie et al. 2004,[26] which assessed satiation (the time to voluntary cessation of eating from a standardised food array after a 12-hour fast) and satiety (the time to hunger sufficient to consume a complete meal after consumption of a standardised preload) in eight female patients with hypoleptinemia, from the NIH 991265/20010769 study. Metreleptin treatment mean (SD) decreased satiation time from 41.2 (18.2) to 19.5 (10.6) min, increased mean (SD) satiety time from 62.9 (64.8) to 137.8 (91.6) min, decreased mean (SD) energy consumed to produce satiation from 2034 (405) to 1135 (432) kcal, and decreased the amount of food desired in the post-absorptive state.[26]

This study is not listed in the included publications provided by the company (see Section 4.2.1, Table 3). The ERG has added the numerical results from this study (not provided in the CS) to the above text.

The CS does not include any data on hyperphagia from the NIH follow-up study. The study report for the NIH follow-up study,[46] provided in response to clarification questions, states only that 'hyperphagia is determined by notes in the medical charts'; no objective measures (e.g. calorie intake or standardised measures of satiation) are reported.[46] At baseline, 57/68 (84%) of GL patients and 31/44 (70%) of PL patients were classified as having hyperphagia.

Similarly, the NIH follow-up study states that 'improvement in hyperphagia is determined by improvement as indicated in post-metreleptin notes' and specifies that patients must have at least one year of post-metreleptin data in order to be included in the improvement count.[46] Based on this definition, 47 (89%) of the 53 GL patients and 25/26 (96%) of PL patients who had hyperphagia at baseline and who had at least one year of post-metreleptin data were classified as having experienced improvements in hyperphagia.[46] Whilst these results appear to indicate that metreleptin treatment is associated with improvements in hyperphagia, it should be noted that no objective measures of hyperphagia were reported and no details were provided about the nature of the hyperphagia information recorded in notes.

ERG comment: The CS did not report any comparator results for hyperphagia and the GL/PL natural history study did not report any information about hyperphagia.[40]

Concomitant medication use

The CS included some information, from the NIH 991265/20010769 study, about discontinuation of insulin, oral antidiabetics, or lipid-lowering therapies following initiation treatment with metreleptin.[1, 37] Sixteen (41%) of 39 patients with GL who were receiving insulin at baseline were able to discontinue insulin use after starting metreleptin and seven (22%) of 32 patients who were receiving oral antidiabetic medications at baseline were able to discontinue use of these drugs. Among the 34 patients who were receiving lipid-lowering therapies at baseline, eight (24%) were able to discontinue these medications.[1, 37] In the PL subgroup, one patient was able to discontinue the use of oral antidiabetic medications and one was able to discontinue the use of lipid-lowering therapies.[1, 37]

ERG comment: The CS also states that: 'Many of these patients could discontinue the use of these therapies within the first 12 months of metreleptin treatment.' However, no times to discontinuation are reported.

The CS does not include any data on concomitant medication use from the NIH follow-up study. The study report for the NIH follow-up study,[46] reported that 57/68 (83.8%) of GL patients and 43/44 (97.7%) of PL patients were on anti-diabetic medication (insulin or oral anti-diabetics) at baseline.[46] A new anti-diabetic medication was initiated (defined as two or more fills of a medication not present at baseline), after the start of metreleptin treatment, in 54/68 (79.4%) of GL patients and 36/44 (81.8%) of PL patients.[46] The equivalent data for lipid lowering medication showed that 28/68 (41.2%) of GL patients and 30/44 (68.2%) of PL patients were on lipid-lowering medication (statin and/or fibrates) at baseline.[46] A new lipid-lowering medication was initiated (defined as two or more fills of a medication not present at baseline), after the start of metreleptin treatment, in 18/68 (26.5%) of GL patients and 27/44 (61.4%) of PL patients.[46] Medication discontinuation was defined as a 12-month period without any medication prescription fills and included both baseline medications and medications initiated after the start of metreleptin treatment; 41/64 (64.1%) of GL patients and 15/44 (34.1%) of PL patients were able to discontinue antidiabetic medications.[46] Most discontinuations were for bolus insulin or metformin, only two GL patients discontinued basal insulin or insulin + metformin.[46] With respect to lipid-lowering medication, 19/35 (54.3% of GL patients and 16/38 (68.2%) of PL patients were able to discontinue lipid lowering

medications.[46] The majority of discontinuations, 26/35, were for fibrates, with few patients discontinuing statin use.[46]

Growth and development

The CS includes some information, from the NIH 991265/20010769 study, about growth and development in metreleptin treated patients.[1, 37] This study assesses stature at screening/baseline and at least one post-baseline time point in 40 children (<18 years of age), including 36 patients with GL and four patients with PL (two in the PL subgroup). Among the 36 GL patients, 22 were reported to have normal stature at study entry, 10 had tall stature for their age, and four had short stature. Overall 16 (44%) of the 36 patients were reported to have had growth complete or near complete prior to entry. Among the other 20 patients, 10 were reported to have normal growth (including five with normal stature, three who were tall and two who were short at baseline), two had growth acceleration (one with normal stature and one with short stature), and eight had growth deceleration (five with normal stature and three who were tall). Among the four PL patients with data available, two patients (in the PL subgroup) had growth complete or near complete at study entry. Among the other two patients, one had short stature at baseline with growth deceleration reported on metreleptin and one had tall stature at baseline with normal growth on metreleptin.[1, 37]

Overall 33 patients <18 years of age had pubertal status assessed at baseline, including 27 patients with GL and six patients with PL (five in the PL subgroup); 26 of these patients had puberty complete, near complete, or probably complete (based on growth data) prior to metreleptin. Among the other seven patients, all with GL, four had delayed puberty prior to metreleptin and three had precocious puberty; follow-up was available for three of these patients, all with delayed puberty at entry (two had normal development on metreleptin and one continued to have delayed puberty). Among the 14 patients without baseline data reported who were not prepubertal (normal for age), 13 reported normal pubertal onset and/or progression on metreleptin at a post-baseline assessment and one had delayed onset reported.[1, 37]

ERG comment: The NIH follow-up study[46] did not report any additional information about the growth and development of metreleptin-treated patients. The GL/PL natural history study[40] does not include any information about growth and development.

Reproductive dysfunction

The clinical effectiveness section of the CS does not include any evidence about the effects of metreleptin treatment on reproductive dysfunction.[1]

ERG comment: Two publications,[58, 61] listed as included publications related to the NIH 991265/20010769 study (see Section 4.2.1, Table 3) reported assessments of the effects of metreleptin treatment on female reproductive dysfunction. In one study, 10 female patients with GL showed a mean (SD) decrease in serum free testosterone from 39.6 (11) to 18.9 (4.5) ng/dL following metreleptin treatment; ovarian ultrasound showed a polycystic ovarian disease pattern in all patients that did not change after therapy, and eight of the 10 patients had amenorrhea prior to therapy and all eight developed normal menses after therapy.[61] The second

study included seven female patients with severe LD; five of these patients had intact reproductive systems and only one was cycling normally at the start of metreleptin treatment, but all five had normal menses by the fourth month of treatment.[58] The results from these two publications were not included in the CS.

The NIH follow-up study[46] also reports information about the effects of metreleptin treatment on female reproductive dysfunction. The report defined disruption to the female reproductive system as the presence of irregular menstruation or polycystic ovary syndrome (PCOS). Female patients are not considered to have disruption to female reproductive function if they are experiencing menopause, are prepubescent, or had surgical removal of reproduction organs. At baseline, 21/27 (78%) of relevant female GL patients and 24/29 (83%) of relevant female PL patients were classified as experiencing reproductive dysfunction.[46] Twelve (57%) of the 21 effected GL patients and eight (33%) of the 24 effected PL patients were reported as having post-metreleptin improvement ('improvement in any of irregular menstruation or PCOS').[46] However, no definition of the criteria used to determine improvement was provided.

The CS did not report any comparator results for reproductive dysfunction (from the GL/PL natural history study); a study report was provided in response to clarification questions and this report includes information about female reproductive dysfunction in LD patients.[40] This report included information on the number of female patients with reproductive dysfunction (including amenorrhea, menstruation <6 times per year, pregnancy loss, infertility or subfertility, ovarian cysts, and PCOS) at baseline, (see Section 4.2.1, Table 6). Over the whole observation period, 2/15 (13.3%) of female GL patients and 15/41 (36.6%) of female PL patients were found to have reproductive dysfunction.[40] Using the reported data for the baseline period and the whole observation period, it is possible to calculate the proportion of patients, who did not have reproductive dysfunction at baseline, but developed problems during the follow-up period (after GL/PL diagnosis). Of the 13 female GL patients who did not have reproductive dysfunction at baseline, nine (69.2%) developed reproductive dysfunction during follow-up and 19/26 (73.1%) of female PL patients who did not have reproductive dysfunction at baseline developed problems during follow-up.

Pancreatitis

The clinical effectiveness section of the CS does not include any information about the effects of metreleptin treatment on pancreatitis; pancreatitis is only reported as an adverse event occurring subsequent to metreleptin withdrawal (CS, section 9.7.2.5, page 114).

ERG comment: The NIH follow-up study[46] reports information about the effects of metreleptin treatment on pancreatitis. A patient was considered to have pancreatitis at baseline if they had ≥1 episodes of pancreatitis in the one year prior to metreleptin initiation.[46] At baseline, 21/63 (31%) of GL patients and 23/44 (52%) of PL patients had a history of pancreatitis.[46] Improvement in pancreatitis was defined as no recorded episodes of pancreatitis post-metreleptin initiation or only episodes of pancreatitis which were due to non-compliance.[46] Based on these criteria, 20/21 (95%) of effected GL patients and all effected PL patients experienced improvements in pancreatitis on metreleptin treatment. These data were not included in the CS, but are of particular importance given the identified risk of pancreatitis

following metreleptin withdrawal; it is important to consider the extent to which this risk may be balanced by any reduction in the incidence of pancreatitis that may occur in patients on treatment.

The CS did not report any comparator results for pancreatitis (from the GL/PL natural history study).[40] This report included information on the number of patients with pancreatic damage (all pancreatitis) at baseline, (see Section 4.2.1, Table 6). Over the whole observation period (including baseline and follow-up), 7/56 (12.5%) of GL patients and 20/122 (16.4%) of PL patients experienced at least one episode of pancreatitis.[40] Five (71.4%) of the 7 effected GL patients and 12/20 (60.0%) of effected PL patients experienced pancreatitis during the follow-up period (after GL/PL diagnosis).

Health-related quality of life including effects on appearance and activities of daily living
The clinical effectiveness section of the CS does not include any information about the effects of metreleptin treatment on measures of health-related quality of life.

ERG comment: The NIH follow-up study[46] reports information about the effects of metreleptin treatment on impaired physical appearance and ability to perform work/school work. Impaired physical appearance was defined as the presence of acanthosis nigricans, hyperkeratosis, or hirsutism; at baseline, 56/68 (82%) of GL patients and 30/44 (68%) of PL patients were classified as having impaired physical appearance.[46] Thirty-eight (68%) of the 56 effected GL patients and 14 (47%) of the 30 effected PL patients were reported as having post-metreleptin improvement ('improvement in any of acanthosis nigricans, hyperkeratosis, or hirsutism').[46] However, no definition of the criteria used to determine improvement was provided. Loss of ability to perform work/school work was defined as incomplete school attendance due to disease symptoms for school age patients or not working/working part-time due to disease symptoms; at baseline 39/68 (57%) of GL patients and 9/44 (20%) of PL patients were effected.[46] Improvement in loss of ability to perform work/school work is defined as complete school attendance for school-age patients or the ability for a patient to work, even if the patient has chosen not to work; 31/39 (79%) effected GL patients and 5/9 (56%) of effected PL patients experienced improvements in their ability to perform work or school work whilst on metreleptin treatment.[46]

The CS did not report any comparator results for impaired physical appearance or ability to perform activities of daily living (from the GL/PL natural history study).[40] This report included information on the numbers of patients characteristics of physical appearance associated with lipodystrophy; only one of the three characteristics included in the NIH follow-up study definition of impaired physical appearance (acanthosis nigricans) was also recorded in the GL/PL natural history study. Acanthosis nigricans was present in 29 (56.9%) of the 51 GL patients and 39 (37.7%) of the 105 PL patients in the GL/PL natural history study, for whom information was available.[40] The GL/PL natural history study did not include any information about the ability of LD patients to perform activities of daily living.

Mortality

Survival data for LD patients, from the GL/PL natural history study[40] and for patients on metreleptin treatment, from the NIH follow-up study[46] are used in the cost effectiveness analyses presented in the CS,[1] but no survival data are presented in the clinical effectiveness section of the CS.

ERG comment: For information, we have reproduced the mortality tables from both the NIH follow-up[46] and GL/PL natural history[40] studies (Tables 17 and 18 below).

Table 17: Mortality and cause of death data from the NIH follow-up study

	All Patients (n=112)	GL Patients (n=68)	PL Patients (n=44)
Age at metreleptin initiation			
Mean (SD)	24.3 (15.4)	17.5 (11.4)	34.6 (15.2)
Median (IQR)	18.2 (14.0, 34.6)	15.4 (11.9, 20.2)	34.6 (18.9, 45.9)
Years from metreleptin initiation to last known status*			
Mean (SD)	8.4 (4.5)	8.8 (4.7)	7.7 (4.2)
Median (IQR)	7.6 (4.5, 11.7)	8.1 (5.3, 12.3)	5.6 (4.3, 10.8)
Age at last known status*			
Mean (SD)	32.6 (16.2)	26.3 (12.9)	42.4 (16.2)
Median (IQR)	27.1 (20.5, 44.7)	24.3 (18.9, 29.2)	42.6 (28.7, 56.2)
Patients still alive, n (%)$			
Yes	94 (83.9)	55 (80.9)	39 (88.6)
No	13 (11.6)	12 (17.6)	1 (2.3)
Uncertain	5 (4.5)	1 (1.5)	4 (9.1)
Years from first GL/PL symptoms to death			
Kaplan-Meier Mean (SE)	15.4 (0.5)	14.7 (0.7)	16.7 (0.3)
Patients who died, n	13	12	1
Age at metreleptin initiation			
Mean (SD)	24.2 (15.3)	23.9 (16.0)	27.7 (NA)
Median (IQR)	17.7 (15.1, 27.7)	17.4 (14.9, 27.7)	27.7 (NA)
Years from metreleptin initiation to death			
Mean (SD)	6.3 (4.9)	6.5 (5.0)	3.4 (NA)
Median (IQR)	4.3 (1.9, 10.6)	4.8 (1.8, 11.2)	3.4 (NA)
Age at death			
Mean (SD)	30.5 (15.6)	30.4 (16.2)	31.2 (NA)
Median (IQR)	25.3 (20.1, 31.2)	24.5 (19.7, 37.4)	31.2 (NA)
Potential contributing factors, n (%)			
End stage liver disease	4 (30.8)	4 (33.3)	0 (0.0)
End stage renal disease	2 (15.4)	2 (16.7)	0 (0.0)
Cardiac failure	2 (15.4)	2 (16.7)	0 (0.0)
Cardiac failure and kidney failure	1 (7.7)	1 (8.3)	0 (0.0)
Hepatorenal failure	1 (7.7)	1 (8.3)	0 (0.0)
Lymphoma	1 (7.7)	1 (8.3)	0 (0.0)
Respiratory failure	1 (7.7)	0 (0.0)	1 (100)
Unknown	1 (7.7)	1 (8.3)	0 (0.0)

GL, generalized lipodystrophy; IQR, interquartile range; NIH, National Institutes of Health; NA, not applicable; PL, partial lipodystrophy; SD, standard deviation; SE, standard error

*Last known status is the latest date in which patient status is known

$Status of patient as of 12/18/2017

Table 18: Mortality and cause of death data from the GL/PL natural history study

	All Patients (n=178)	GL Patients (n=56)	PL Patients (n=122)
Years from first GL/PL symptoms to end of observation period*			
Mean (SD)	14.7 (13.3)	12.7 (10.5)	15.5 (14.4)
Median (IQR)	10.0 (3.9, 21.4)	10.1 (3.5, 18.0)	9.6 (4.0, 23.1)
Years from first GL/PL symptoms to diagnosis			
Mean (SD)	8.0 (11.4)	3.9 (7.4)	9.8 (12.5)
Median (IQR)	2.5 (0.0, 12.0)	0.0 (0.0, 3.8)	5.0 (0.0, 15.9)
Patients still alive, n (%)			
Yes	142 (79.8)	37 (66.1)	105 (86.1)
No	14 (7.9)	8 (14.3)	6 (4.9)
Unknown	22 (12.4)	11 (19.6)	11 (9.0)
Years from first GL/PL symptoms to death**			
Kaplan-Meier Mean (SE)	48.0 (2.2)	29.8 (1.8)	52.5 (1.9)
Median (IQR)	56.3 (34.5, NR)	31.7 (30.7, NR)	56.3 (56.3, NR)
Patients who died, n	14	8	6
Age at first GL/PL symptoms			
Mean (SD)	24.9 (21.2)	16.9 (20.6)	35.6 (18.3)
Median (IQR)	20.5 (6.5, 49.5)	8.3 (2.3, 32.1)	29.7 (26.0, 55.4)
Age at death			
Mean (SD)	45.3 (17.2	38.2 (16.0)	54.8 (14.8)
Median (IQR)	42.0 (31.3, 62.5)	31.7 (28.2, 52.4)	57.9 (39.5, 69.0)
Death related to lipodystrophy, n (%)			
Yes	7 (50.0)	6 (75.0)	1 (16.7)
No	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	7 (50.0)	2 (2.0)	5 (83.8)
Patients who died, n	14	8	6
Cause of death reported,[$] n (%)	10 (71.4)	8 (100)	2 (33.3)
Method of assessing cause of death, n (%)			
Per practice health records	3 (21.4)	1 (12.5)	2 (33.3)
Per physician recollection	5 (35.7)	4 (50.0)	1 (16.7)
From death certificate	2 (14.3)	2 (25.0)	0 (0.0)
Not confirmed	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	4 (28.6)	1 (12.5)	3 (50.0)
Potential contributing factors, n (%)			
Bone marrow/hematologic abnormalities	0 (0.0)	0 (0.0)	0 (0.0)
Cancer	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular event	4 (28.6)	3 (37.5)	1 (16.7)
Cerebrovascular disease	3 (21.4)	1 (12.5)	2 (33.3)
Immunosuppression	1 (7.1)	1 (12.5)	0 (0.0)
Infection (viral)	0 (0.0)	0 (0.0)	0 (0.0)
Infection (bacterial)	1 (7.1)	1 (12.5)	0 (0.0)
Liver disease	3 (21.4)	2 (25.0)	1 (16.7)
Pancreatitis	1 (7.1)	1 (12.5)	0 (0.0)
Pneumonia	1 (7.1)	1 (12.5)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	5 (35.7)	1 (12.5)	4 (66.7)

	All Patients (n=178)	GL Patients (n=56)	PL Patients (n=122)
Other[$$]	1 (7.1)	1 (12.5)	0 (0.0)
Location where patient died, n (%)			
At home	1 (7.1)	1 (12.5)	0 (0.0)
At the hospital	7 (50.0)	5 (62.5)	2 (33.3)
Unknown	5 (35.7)	1 (12.5)	4 (66.7)
Other	1 (7.1)	1 (12.5)	0 (0.0)

[*]The end of the observation was defined as the earliest of: date of chart abstraction; death; loss to follow-up
[**]In order to account for censoring due the end of data availability, the average time to death was calculated using the Kaplan-Meier estimate
[$]Causes of death included mentions of cardiac arrest, death following coronary artery bypass graft, diabetic foot infection, heart failure related to valvular stenosis, hospitalisation for kidney failure, multiple diagnoses (atypical interstitial pneumonitis, progressive CGL with insulin resistance, hepatosplenomegaly, thrombocytopenia, polycythemia, acanthosis nigricans, hypertriglyceridemia), myocardial infarction, possible cardiac episode, probable end stage liver disease, and stroke
[$$]Other potential contributing factors of death included mentions of pancytopenia, steatohepatitis, and chronic renal insufficiency

Safety and tolerability

The CS states that the safety profile of metreleptin in patients with LD is consistent with that of a patient population with significant co-morbidities.[1] The CS further states that long-term exposure available from clinical trials across a relatively large population of patients with this ultra-rare disease provides guidance on the expected safety profile of this agent intended for chronic therapy in patients with GL and in a subgroup of patients with PL who have more significant baseline metabolic disturbances of HbA_{1c} ≥6.5% and triglycerides ≥5.65 mmol/L.[1]

The CS refers to further data from the post-marketing period from 138 patients who have been exposed worldwide to commercially available metreleptin (including 116 in the US and 22 in Japan) has shown a safety profile that is consistent with that observed in clinical trials with no new safety signals identified. The identified risks of hypersensitivity, acute pancreatitis associated with metreleptin discontinuation, and hypoglycaemia with concomitant use of insulin and insulin secretagogues can be managed with risk communication in labelling and educational activities.[33, 37, 38] The CS states that in conclusion, the known side effects of metreleptin can be managed as part of the normal clinical practice for patients with this complex condition.

ERG comment: The CS does not include any mention of the safety concerns highlighted in the Centre for Drug Evaluation and Research Report (not included in the CS) or the associated Risk Evaluation Management Strategy (REMS).[75] The summary of safety in this report states: 'The principal safety concerns with metreleptin are T-cell lymphoma and anti-metreleptin antibodies with neutralizing activity. These concerns are of sufficient magnitude to require REMS. Other safety findings that warrant inclusion in the Warning and Precautions section of the metreleptin labelling include hypoglycemia, autoimmunity, and hypersensitivity.'

The CS provides no reference for the data described as post-marketing period from 138 patients who have been exposed worldwide to commercially available metreleptin (including 116 in the US and 22 in Japan).[1]

Adverse events

Study NIH 991265/20010769

A summary of treatment-emergent adverse events (TEAEs) is shown in Table 19, below (reproduced from the CS, Table C25, pages 108-109).[1] In the GL group, 59 (89%) of the 66 patients reported at least one TEAE; drug-related TEAEs were reported in 32 (49%) of these patients.[37] Compared with the GL group, the overall incidence of TEAEs was similar in the PL subgroup with 27 (87%) of the 31 patients experiencing at least 1 TEAE; the incidence of drug-related TEAEs was lower (23%).

TEAEs of severe intensity were reported in 29 (44%) of the 66 GL patients and in 13 (42%) of the 31 patients in the PL subgroup; most severe TEAEs were assessed as unrelated to study treatment.[37]

Overall, 23 (35%) of the 66 GL patients and 7 (23%) of the 31 patients in the PL subgroup experienced a treatment-emergent SAE.[37] The types of SAEs were consistent with the underlying LD disease, and primarily included reports of abdominal pain and pancreatitis, infections, and worsening liver function. Drug-related SAEs were not common, reported in three GL patients, including one case of hypertension, one of respiratory distress and one case of anaplastic large-cell lymphoma. None of the patients in the PL subgroup experienced a drug-related SAE.

Discontinuations due to TEAEs were reported in five patients with GL (8%) and one patient in the PL subgroup (3%). In four of these six patients, the events leading to withdrawal led to death.[37]

The majority of the commonly reported events in the GL group were consistent with the expected pharmacologic effects of metreleptin, including weight loss, hypoglycaemia, and decreased appetite, or were gastrointestinal (GI) disorders or constitutional symptoms, including abdominal pain and headache.[37] Other commonly reported GI disorders in patients with GL included nausea and constipation. The most commonly reported drug-related TEAEs in GL patients were weight decreased (15 patients, 23%) and hypoglycaemia (eight patients, 12%).

In general, the safety profile in the PL subgroup was consistent with that observed in the overall GL group. The most common TEAEs reported in the PL subgroup were abdominal pain, hypoglycaemia, nausea, fatigue, alopecia and constipation. The most commonly reported drug-related TEAEs in patients in the PL subgroup were hypoglycaemia and fatigue (each three patients, 10%).[37]

Table 19: Adverse events: study NIH 991265/20010769 (safety analysis set)

	GL (N = 66)	PL subgroup[a] (N = 31)	PL overall (N = 41)
Overall Summary			
TEAE	59 (89.4)	27 (87.1)	35 (85.4)
Drug-related TEAE	32 (48.5)	7 (22.6)	8 (19.5)
Severe TEAE	29 (43.9)	13 (41.9)	16 (39.0)
Drug-related severe TEAE	7 (10.6)	0	0
Treatment-emergent SAE	23 (34.8)	7 (22.6)	10 (24.4)
Drug-related treatment emergent SAE	3 (4.5)	0	0
TEAE leading to study drug discontinuation	5 (7.6)	1 (3.2)	1 (2.4)
On-study deaths	3 (4.5)	1 (3.2)	1 (2.4)
Most common (≥5% Incidence overall) TEAE			
Weight decreased	17 (25.8)	2 (6.5)	2 (4.9)
Abdominal pain	11 (16.7)	6 (19.4)	6 (14.6)
Hypoglycaemia	10 (15.2)	6 (19.4)	7 (17.1)
Decreased appetite	8 (12.1)	1 (3.2)	1 (2.4)
Headache	8 (12.1)	0	0
Nausea	6 (9.1)	5 (16.1)	6 (14.6)
Fatigue	6 (9.1)	3 (9.7)	3 (7.3)
Ear infection	6 (9.1)	0	0
Arthralgia	6 (9.1)	2 (6.5)	3 (7.3)
Upper respiratory tract infection	5 (7.6)	1 (3.2)	2 (4.9)
Back pain	5 (7.6)	2 (6.5)	2 (4.9)
Anxiety	5 (7.6)	0	1 (2.4)
Proteinuria	5 (7.6)	0	1 (2.4)
Ovarian cyst	5 (7.6)	0	1 (2.4)
Depression	4 (6.1)	1 (3.2)	3 (7.3)
Alopecia	3 (4.5)	3 (9.7)	3 (7.3)
Constipation	3 (4.5)	3 (9.7)	3 (7.3)
Pain in extremity	3 (4.5)	2 (6.5)	3 (7.3)

Abbreviations: GL = generalised lipodystrophy; PL = partial lipodystrophy; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] PL subgroup = patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

ERG comment: The CS states that the total patient-years of exposure for GL patients was 328.3 years and the median actual duration of treatment (excluding dose interruptions) was 47.2 months.[1, 37] The total patient-years of exposure for PL subgroup patients was 121.3 years and the median actual duration of treatment (excluding dose interruptions) was 29.3 months.[1, 37] The CSR for the NIH 991265/20010769 study also notes that: All but one (>99%) of the 107 patients in the safety analysis set (SAS) received six months or more of metreleptin treatment, with 87% (93 patients) receiving >1 year, 72% (77 patients) receiving >2 years, and 54% (58 patients) receiving >3 years of metreleptin. More than one quarter of patients (28%, 30 patients), received more than six years of treatment with metreleptin with 13 (12%) on treatment for 10 years or more.[74] The timescale over which adverse events was reported is not explicitly stated in the CS, but CSR indicates that patients in the SAS received ongoing at six month exposure intervals.[74]

The CS states that overall, 23 (35%) of the 66 GL patients and 7 (23%) of the 31 patients in the PL subgroup experienced at least one serious adverse event (SAE). This appears to be an error as the numbers refer to treatment-emergent SAE not overall SAE. The CS states that in general, the safety profile in the PL subgroup was consistent with that observed in the overall GL group.[1] The ERG group disagrees. In the GL group weight decrease was a TEAE in 25.8% whereas it was 6.4% in the PL subgroup. Similarly, decreased appetite was a TEAE in 12.1% of the GL group and in 6.4% of the PL subgroup. In addition, the ERG would argue that weight decrease in 25.8% of GL group is an undesirable adverse event given the loss of adipose tissue associated with the condition.

Study FHA101

A summary of TEAEs is shown in Table C26 (pages 111-112 of the CS) and replicated in Table 20, below[1].

In the GL group, seven (78%) of the nine patients reported at least one TEAE; drug-related TEAEs were reported in six (67%) of these patients.[38] All seven patients in the PL subgroup experienced at least one TEAE, and TEAEs were assessed as drug-related in six (86%) of these seven patients.

In six (67%) of the nine patients with GL, events of severe intensity were reported. All TEAEs in the PL subgroup were mild to moderate in severity.[38] Among the PL patients not included in the PL subgroup, events of severe intensity were reported in nine (36%) of the 25 patients.

Overall, six (67%) of the nine GL patients experienced at least one SAE, none of which was assessed as related to study treatment.[38] There were no SAEs reported in patients in the PL subgroup. Ten patients with PL who were not in the PL subgroup experienced SAEs.

Discontinuations due to TEAEs were reported in the two patients who died and in two additional patients with PL (not in the PL subgroup).[38]

In general, when considering the difference in sample size, the types and incidence for commonly reported TEAEs in study FHA101 were similar to those reported in the pivotal study

NIH 991265/20010769. Among the nine patients with GL in Study FHA101, the most commonly reported TEAEs, all reported in two patients (22%), were hypoglycaemia, upper respiratory tract infection, abdominal pain, increased liver function tests, and ear infection.[38] For the seven patients in the PL subgroup, the most commonly reported TEAEs were hypoglycaemia, upper respiratory tract infection, and urinary tract infection (each three patients, 43%), and nausea, anxiety, and sinusitis (each two patients, 29%). The only drug-related TEAE reported in more than one GL patient was hypoglycaemia (two patients, 22%). In the PL subgroup, the only drug-related TEAEs reported in more than one patient were hypoglycaemia and nausea (each two patients, 29%).

Table 20: Adverse events: Study FHA101 (safety analysis set)

	GL (N = 9)	**PL subgroup[a] (N = 7)**	**PL overall (N = 32)**
Overall summary			
TEAE	7 (77.8)	7 (100.0)	27 (84.4)
Drug-related TEAE	6 (66.7)	6 (85.7)	22 (68.8)
Severe TEAE	6 (66.7)	0	9 (28.1)
Drug-related severe TEAE	0	0	2 (6.3)
Treatment-emergent SAE	6 (66.7)	0	10 (31.3)
Drug-related treatment emergent SAE	0	0	1 (3.1)
TEAE leading to study drug discontinuation	1 (11.1)	0	3 (9.4)
On-study deaths	1 (11.1)	0	1 (3.1)
Most common (≥5% incidence overall) TEAE (MedDRA preferred term)			
Hypoglycaemia	2 (22.2)	3 (42.9)	11 (34.4)
Upper respiratory tract infection	2 (22.2)	3 (42.9)	6 (18.8)
Urinary tract infection	1 (11.1)	3 (42.9)	6 (18.8)
Nausea	1 (11.1)	2 (28.6)	12 (37.5)
Anxiety	1 (11.1)	2 (28.6)	2 (6.3)
Sinusitis	0	2 (28.6)	2 (28.6)
Liver function test increased	2 (22.2)	1 (14.3)	1 (3.1)
Abdominal pain	2 (22.2)	1 (14.3)	5 (15.6)
Vomiting	1 (11.1)	1 (14.3)	4 (12.5)

	GL (N = 9)	PL subgroup[a] (N = 7)	PL overall (N = 32)
Headache	1 (11.1)	1 (14.3)	4 (12.5)
Injection site bruising	1 (11.1)	1 (14.3)	4 (12.5)
Lymphadenopathy	1 (11.1)	1 (14.3)	3 (9.4)
Dizziness	0	1 (14.3)	3 (9.4)
Muscle spasms	0	1 (14.3)	6 (18.8)
Myalgia	0	1 (14.3)	3 (9.4)
Viral infection	0	1 (14.3)	3 (9.4)
Ear infection	2 (22.2)	0	1 (3.1)
Dyspnoea	1 (11.1)	0	2 (6.3)
Vertigo	0	0	4 (12.5)
Injection site pruritus	0	0	3 (9.4)

Abbreviations: GL = generalised lipodystrophy; PL = partial lipodystrophy; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] PL subgroup = PL subgroup = patients with baseline leptin <12 ng/mL and HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

ERG comment: The CS describes the total patient-years of exposure for GL patients was 11.3 years and the median actual duration of treatment (excluding dose interruptions) was 21.3 months.[1, 37] The total patient-years of exposure for PL subgroup patients was 28.4 years and the median actual duration of treatment (excluding dose interruptions) was 51.3 months.[1, 37] The CSR for the FH101 study also notes that: Overall, 35 (88%) of the 40 patients with data available for exposure received six months or more of metreleptin treatment with 70% (28 patients) receiving >1 year, 45% (18 patients) receiving >2 years, and 35% (14 patients) receiving >3 years of metreleptin in this study. Overall, four patients (10%), received more than five years of treatment with metreleptin.[76] The timescale over which adverse events was reported is not explicitly stated in the CS, but CSR indicates that patients in the safety population received ongoing at six month exposure intervals.[76]

The CS states that overall, six (67%) of the nine GL patients experienced at least one serious adverse event (SAE)[1]. This appears to be an error as the numbers refer to treatment-emergent SAE not SAE.

Paediatric population

The CS reported safety and tolerability with respect to the paediatric population.[1] The CS states that across the two completed clinical studies (NIH 991265/20010769 and FHA101), there were 50 paediatric subjects (five in the PL subgroup and 45 with GL) enrolled and exposed to metreleptin. Limited clinical data exists in children less than six years old.[33]

The CS reports that the overall, the safety and tolerability of metreleptin are similar in children and adults.[1] In GL patients, the overall incidence of drug related adverse reactions was similar

regardless of age. SAEs were reported in 15 paediatric patients, primarily reports of abdominal pain and pancreatitis (each three patients), and pneumonia and liver disorder (each two patients).[33] The only common TEAEs reported at a higher incidence (≥10% difference) in patients ≥6 to <18 years compared to adults were abdominal pain (25% vs 5%) and nausea (15% vs 0%).[33] In PL patients, assessment across age groups is limited, due to the small sample size.[33] However, there were no apparent differences in the overall incidence or the incidence of common adverse events between age categories.[33]

ERG comment: The CS only mentions the paediatric population from the NIH 991265/20010769 study (five in the PL subgroup and 45 with GL). It omits the three paediatric patients who have PL but do not meet the subgroup criteria (patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L). The CS also omits the paediatric population from the FHA101 study. A further three paediatric subjects (in GL) were enrolled and exposed to metreleptin in FHA101.[38]

The CS includes additional information concerning 'selected adverse reactions' (CS, section 9.7.2.5, pages 114-116).[1]

Pancreatitis

Across the 148 patients included in LD studies, six (4%) patients (four with GL and two with PL), experienced treatment emergent pancreatitis.[33, 37, 38] All patients had a history of pancreatitis and hypertriglyceridemia.[33, 37, 38] One of the patients who developed septic shock concurrent with pancreatitis died; the other five patients recovered and continued on treatment.[33, 37, 38] Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridemia.[33]

ERG comment: The CS describes abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. Tables C18 and C19 (pages 86-87 of the CS) describe the number of premature discontinuations in study NIH 991265/20010769 and study FHA101 respectively.[1] In Table C18 23/66 (34.8%) GL patients; 15/41 (36.6%) PL patients and 11/31 (35.5%) PL subgroup patients prematurely discontinued. In Table C19 4/9 (44.4%) GL patients; 20/32 (62.5%) PL patients and 2/7 (28.6%) PL subgroup patients prematurely discontinued. The numbers of patients who discontinue treatment are alarmingly high given that discontinuation of treatment appears to be associated with an increased risk of pancreatitis.

The Centre for Drug Evaluation and Research Report (not included in the CS),[75] includes the following statement: 'The sponsor argues that the patients who developed pancreatitis were either non-compliant or they discontinued metreleptin therapy too rapidly and induced a rebound in serum TG levels. Dr Golden was unable to confirm the sponsor's assertion and rightly points out that the lack of a control group and the small size of the lipodystrophy database leave unanswered the question of metreleptin's role in the cases of pancreatitis.'

Serious infections

A significant number of patients with acquired forms of LD have low C3 levels and the presence of polyclonal immunoglobulin C3 nephritic factor, increasing the risk for recurrent bacterial infections.[6, 12]

A review of available literature was undertaken to understand the propensity as well as the rate of development of serious infection in patients with LD. The conclusion of this review was that the natural history of patients with LD with low leptin levels is to experience higher rates of infection than the general population.[29, 77-80]

In study NIH 991265/20010769, serious infections were reported in seven (11%) of 66 patients with GL and in two (7%) of 31 patients in the PL subgroup.[37]. The only serious infections reported in more than one patient in the GL group were sepsis and pneumonia, each reported in two patients (3%). In the PL subgroup, serious infections included cellulitis, streptococcal infection, and pharyngitis in one patient and osteomyelitis and cellulitis in the other. All serious infections were assessed as unrelated to study treatment and none led to treatment discontinuation. In study FHA101, no serious infections were reported in the GL group or in the PL subgroup.[38]

ERG comment: The CS[1] states that the natural history of patients with LD with low leptin levels is to experience higher rates of infection than the general population and cites Mancuso 2002 amongst others.[78] Mancuso 2002 is a study of leptin-deficient mice and cannot be cited as evidence in humans.[78] Moon 2013 is also cited in support of patients with LD with low leptin levels who experience higher rates of infection than the general population.[79] Moon 2013 describes leptin's Role in lipodystrophic and nonlipodystrophic Insulin-Resistant and Diabetic Individuals and does not contain any direct evidence in support of this claim.[79]

Hypoglycaemia

Metreleptin may decrease insulin resistance in diabetic patients, resulting in hypoglycaemia in patients with LD and co existing diabetes.[33] Hypoglycaemia, deemed as related to metreleptin treatment, occurred in 13.3% of patients studied. All reports of hypoglycaemia in patients with GL and in the PL subgroup, have been mild in nature with no pattern of onset or clinical sequelae.[33] Generally the majority of events could be managed by food intake with only relatively few modifications of anti-diabetic medicine dosage occurring.[33]

T cell lymphoma

Three cases of T cell lymphoma have been reported while taking metreleptin in clinical studies.[33] All three patients had acquired GL. Two of these patients were diagnosed with peripheral T cell lymphoma while receiving the medicinal product. Both had immunodeficiency and significant haematological abnormalities including severe bone marrow abnormalities before the start of metreleptin treatment. A separate case of anaplastic large cell lymphoma was reported in a paediatric patient receiving the medicinal product who did not have haematological abnormalities before treatment.

ERG comment: The Centre for Drug Evaluation and Research Report (not included in the CS), notes that *in-vitro* and *in-vivo* data indicate that leptin, through activation of tumor-associated leptin receptors, can influence the growth and progression of malignant cells, and includes the following statement: 'According to our colleagues in the Division of Hematology Products, the incidence of T-cell lymphoma in the general population from the United States is 2.3 per 100,000 for males and 1.4 per 100,000 for females. While the incidence of lymphoma in patients from the NIH and FHA101 clinical studies was 5,900 per 100,000 in males and 1,900 per 100,000 in females, these crude estimates are based on a very small sample of patients and therefore have very wide confidence intervals. Moreover, in addition to not knowing if lipodystrophy itself may be associated with an increased risk for lymphoma, two of the three cases of lymphoma were confounded by histories of neutropenia and treatment with G-CSF. Nevertheless, the clinical review team considers the T-cell lymphoma data sufficient to warrant a boxed warning.'[75]

Immunogenicity (neutralising antibodies)

In clinical trials (studies NIH 991265/20010769 and FHA101), the rates of antidrug antibodies (ADAs) for GL patients and the PL subgroup patients were 96% (51 out of 53 patients) and 93% (27 out of 29 patients), respectively.[33]

Overall, in patients where antibody data was available, neutralising ADA activity was observed in 38/102 patients (37%): 25/53 (47%) with GL and 6/29 patients (21%) within the PL subgroup. An attenuation (typically denoted by initial improvement and then decline of both HbA_{1c} and triglyceride levels) and worsening (denoted by decline from baseline in both HbA_{1c} and triglycerides) of metreleptin effect was reported in patients with PL and GL, both with and without neutralising ADAs. In the majority of patients with neutralising activity and apparent attenuation or worsening of metreleptin effect, this effect was transient and without clinical impact.

Serious and/or severe infections that were temporally associated with neutralising activity occurred in five GL patients.[33] These events included one episode in one patient of serious and severe appendicitis, two episodes in patients of serious and severe pneumonia, a single episode of serious and severe sepsis and non-serious severe gingivitis in one patient and six episodes of serious and severe sepsis or bacteraemia and one episode of non-serious severe ear infection in one patient. One serious and severe infection of appendicitis was temporally associated with neutralising activity in a patient with PL who was not in the PL subgroup (i.e. not the indicated population but with a similar safety profile). None of these temporally associated infections were considered related to metreleptin treatment by the study investigators. LD patients with neutralising antibodies and concurrent infections responded to standard of care treatment.

Of the 38 patients with neutralising activity 58% achieved resolution of neutralising antibodies, including 15 patients with GL and seven patients with PL, and 87% (33/38) received uninterrupted metreleptin dosing throughout the period of neutralising activity.[33]

ERG comment: The Centre for Drug Evaluation and Research Report (not included in the

CS), included the following text concerning immunogenicity:

'Metreleptin is highly immunogenic; almost all patients, including those from the obesity development programs, treated with this protein developed binding antibodies. Of greatest immunogenic concern is the potential development of neutralizing antibodies, with resultant inhibition of endogenous leptin activity or loss of efficacy in patients with lipodystrophy.

The sponsor used the following categorization for neutralizing activity from their in-vitro assay: Category A: result is less than the assay cut-point on initial testing; Category B: result is higher than the assay cut-point on initial testing, but less than assay cut-point on repeat testing; Category C: result is higher than the assay cut-point on initial testing and re-testing, but is less than the assay cut-point after additional 1:10 dilution; Category D: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 dilution but not after 1:100 dilution; and Category E: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 and 1:100 dilutions. Categories D and E represent high potency neutralizing activity to metreleptin. Seven patients from the NIH and FHA101 studies developed neutralizing antibody activity (categories D or E). One of these patients had loss of efficacy, as indicated by an increase in HbA_{1c} concentrations, and five hospitalizations due to bacterial infections. A second patient, also with a history of hospitalization for sepsis and worsening glycaemic control, was recently reported to have developed neutralizing activity. These cases raise concern that development of neutralizing antibodies to metreleptin could impair metabolic control and immune function.

The clinical ramifications of developing neutralizing antibodies are not well characterized; yet, the potential risks of worsening metabolic control and/or severe infections in metreleptin treated patients with lipodystrophy led the clinical review team to recommend that this information be included in a boxed warning.'[75]

Injection site reactions

Injection site reactions were reported in 3.5% of patients with LD treated with metreleptin.[33] All events reported in clinical studies in patients with LD have been mild or moderate in severity and none have led to treatment discontinuation. Most events occurred during the initial 12 months of initiation of metreleptin.

All events reported in clinical studies in patients with LD have been mild or moderate in severity and none have led to treatment discontinuation.

ERG comment: The Centre for Drug Evaluation and Research Report (not included in the CS),[75] included additional information on immune-related adverse reactions (hypersensitivity): 'In the NIH trials, 15% of patients experienced 13 reactions that could be considered immune-related. These included urticaria (2.8%), anaphylactic reaction (1.4%), and papular rash (1.4%). In study FHA101, 32% of patients experienced 13 reactions that could be considered immune-related. These included urticaria, swelling face, rash, pruritus, injection site inflammation, injection site pruritus, and injection site urticaria.'

Deaths

Study NIH 991265/20010769

A summary of treatment emergent deaths is shown in Table C25 of the CS (page 109) and replicated in Table 21, below[1].

The CS states[1] that over the 14-year study duration, treatment-emergent deaths were reported in four (4%) of the 107 patients, including three patients with GL and one patient in the PL subgroup.[37] TEAEs leading to death included renal failure, cardiac arrest (concurrent with pancreatitis and septic shock), progressive end-stage liver disease (chronic hepatic failure), and hypoxic-ischaemic encephalopathy. None of the deaths were assessed as drug-related.

Discontinuations due to TEAEs were reported in five patients with GL (8%) and one patient in the PL subgroup (3%). In four of these six patients, the events leading to withdrawal led to death.[37]

Table 21: On-study deaths, study NIH 991265/20010769 (safety analysis set)

	GL (N = 66)	PL subgroup[a] (N = 31)	PL overall (N = 41)
On-study deaths	3 (4.5)	1 (3.2)	1 (2.4)

Abbreviations: GL = generalised lipodystrophy; PL = partial lipodystrophy; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] PL subgroup = patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

Study FHA101

A summary of treatment emergent deaths is shown in Table C26 (page 111 of the CS) and replicated in Table 22, below[1].

Two (5%) of the 41 patients died during study FHA101, including one patient with GL and one with PL (not in the PL subgroup).[38] The cause of death was progression of pre-existing adenocarcinoma in one patient and loss of consciousness following a fall in her home in another. Neither of the deaths was assessed as drug-related.

Discontinuations due to TEAEs were reported in the two patients who died and in two additional patients with PL (not in the PL subgroup).[38]

Table 22: On-study deaths, study FH101 (safety analysis set)

	GL (N = 9)	PL subgroup[a] (N = 7)	PL overall (N = 32)
On-study deaths	1 (11.1)	0	1 (3.1)

Abbreviations: GL = generalised lipodystrophy; PL = partial lipodystrophy; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] PL subgroup = PL subgroup = patients with baseline leptin <12 ng/mL and HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L

4.3 Summary of evidence presented in other submissions

No other scientific evidence was submitted by other consultees. This ERG report does not include a detailed discussion of non-scientific opinion submitted by other consultees or expert testimony provided by other consultees to the appraisal process. Only one submission, from diabetes UK, was made to NICE.

4.4 Additional work on clinical effectiveness undertaken by the ERG

Additional work on clinical effectiveness undertaken by the ERG has been included in Section 4.2.4 of this report. No further additional work was undertaken by the ERG.

4.5 Conclusions of the clinical effectiveness section

4.5.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The ERG is confident that all relevant published studies of metreleptin were identified in the CS, however there were some weaknesses in the methods used to identify unpublished data. However, not all of the relevant studies identified were included in the CS and some relevant outcomes from the studies that were included were not reported.

Importantly, the follow-up study (NIH follow-up) to the main study used in the CS (NIH 991265/20010769) was not included in the CS, even though this study was used in the cost effectiveness analyses presented.

The search strategies reported in the CS did not include any terms for comparators and would only have retrieved studies of the intervention metreleptin. The ERG is, therefore, not confident that the all relevant comparator and natural history studies were identified and considered for inclusion in the CS. Comparator data for the cost effectiveness analyses were based on a single un-published study (GL/PL natural history study) which, as with the NIH follow-up study, was not included in the CS. From the information provided, the ERG cannot be confident that this study represents the best available source of comparator data.

4.5.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The key issue limiting the robustness of the efficacy data presented in the CS is the lack of any comparative studies; estimates of treatment effects are based on changes from baseline in single arm metreleptin treatment studies. This problem is compounded as the CS does not include any attempt to draw indirect comparisons through studies of the effects of established clinical management (diet, lifestyle modifications, lipid lowering drugs and anti-diabetic medications). The natural history study, used to provide comparator data for the cost effectiveness analysis, is not used in the clinical effectiveness sections of the CS and has a population which is not comparable to those included in the metreleptin intervention studies. It is therefore not possible to assess the extent to which any apparent treatment effects are attributable to metreleptin, or whether similar effects could be achieved using standard care.

A further substantive issue concerns the nature of the treatment effects reported. The CS focuses primarily on changes in surrogate outcome measures (e.g. HbA_{1c}, triglycerides, hepatic enzymes) and includes very little information about any effects of treatment on patient-perceived symptoms and clinical outcomes (e.g. hyperphagia, organ damage). The report of the NIH follow-up study,[46] provided in response to clarification questions states that:

'The National Institutes of Health (NIH) Follow-Up study serves as a follow up to the metreleptin clinical trial. This study has allowed for consideration of longer history and follow-up across a range of outcomes not fully studied in the clinical trial. The study is intended to describe the patients who have taken metreleptin at the NIH experiences with lipodystrophy both before and after metreleptin initiation, including outcomes such as hyperphagia, female reproductive dysfunction, damage to key organ systems, and death, as well as trial reported outcomes such as leptin, triglyceride, and glycated haemoglobin (HbA_{1c}) levels.'

and includes the stated objective:

'Describe the outcome of metreleptin on patient health, such as organ damage, hyperphagia, female reproductive dysfunction, death, and metabolic status measures such as leptin, triglyceride, and HbA_{1c} levels.'

However, the 'post-metreleptin improvements' reported in this study are frequently based on measures taken at one year and use definitions based on changes in surrogate outcome measures; for example, improvement in liver abnormality is defined as 20% reduction in ALT/AST at year in a patient who had elevated ALT/AST at baseline. Since changes in ALT/AST from baseline to one year are reported in the main NIH 991265/20010769,[37] the presentation of these data in the NIH follow-up study does not provide additional information about organ damage, but is rather a different way of presenting the same data.

Whilst it may appear reasonable to assume that improvements in surrogate outcomes, such as HbA_{1c}, triglycerides and hepatic enzymes, are likely to predict long-term impacts on future health (e.g. in terms of development of cardiovascular disease, liver cirrhosis and pancreatitis). It should be noted that improvements in these measures are not, in themselves, evidence of a treatment effects on long-term health outcomes. Furthermore, where links between these measures and long-term health outcomes are generally accepted, the evidence underpinning such links was derived from populations very different from the LD population.

4.5.3 Uncertainties surrounding the clinical effectiveness

There is considerable uncertainty about the long-term effects of metreleptin treatment, particularly in relation to patient-perceived symptoms and clinical outcomes. A limited report of the NIH follow-up study,[46] provided in response to clarification questions, included some information on newly emergent (on metreleptin treatment) lipodystrophy characteristics in patients with no evidence of these characteristics prior to metreleptin initiation. However, no indication of the timeframe of observation was provided. The ERG has added these data to the results section of this report (see section 4.2.4). Broadly, these data indicate that new incidences of organ abnormalities (liver, kidney and heart) and female reproductive dysfunction continue to occur, in all categories of LD patient, on metreleptin treatment. The data presented are insufficient to allow an adequate assessment of how the rate of development of new abnormalities on metreleptin treatment would compare with that seen in patients on standard care.

Despite the statement in the CS (section 6.2, page 42) that the EAP, which includes some UK patients at Addenbrooke's Hospital, has been running for over 10 years, no data from the EAP were included in the CS and no explanation for this was provided in either the CS or the company's response to clarification questions.

The CS includes some information on the persistence (up to 36 months) of changes in HbA_{1c} and triglycerides on metreleptin treatment (see section 4.2.4). These data indicate that the apparent effect of metreleptin on triglyceride levels may not be applicable to the overall PL population.

The CS (section 9.7.2.5, pg 114) describes incidences of pancreatitis as an adverse event, following withdrawal from treatment: **'**Across the 148 patients included in LD studies, 6 (4%) patients (4 with GL and 2 with PL), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and hypertriglyceridemia. One of the patients who developed septic shock concurrent with pancreatitis died; the other 5 patients recovered and continued on treatment. Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridemia.'[1] Non-compliance rates of between 9% and 19% were reported,[1] and the extent of the pancreatitis risk, for these patients, remains unclear. Similarly, the results for the NIH 991265/20010 study,[37] described in the CS, note the exclusion of an 'outlier' patient in whom an increase from baseline in triglycerides of >1000% at Month 12/LOCF was observed. This increase was attributed to non-compliance; the extent to which such large increases in triglycerides may be seen in patients who withdraw abruptly from metreleptin is unclear, and similarly the persistence and long-term consequences of any such increases is unknown.

With respect to safety and adverse events, the CS concludes that the known side effects of metreleptin can be managed as part of the normal clinical practice for patients with this complex condition. The CS does not report the safety concerns as highlighted in the Centre for Drug Evaluation and Research Report (not included in the CS) or the associated REMS.[75] The summary of safety in this report states: 'The principal safety concerns with metreleptin are T-cell lymphoma and anti-metreleptin antibodies with neutralizing activity. These concerns are of sufficient magnitude to require REMS. Other safety findings that warrant inclusion in the Warning and Precautions section of the metreleptin labelling include hypoglycemia, autoimmunity, and hypersensitivity.'[75]

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

This chapter aims to provide an assessment of whether or not metreleptin for lipodystrophy represents value for money for the NHS in England. The main source of evidence used to inform this assessment is the CS to NICE, which includes a cost effectiveness model and description of the methods and results of an economic analysis using the submitted model. This chapter first looks at other economic analyses of metreleptin or other treatments for lipodystrophy available either from the literature or elsewhere in the public domain. This is followed by a detailed exposition and critique of the submitted model and accompanying economic analysis. Due to the concerns of the ERG with respect to the credibility of the submitted model, Chapter 6 includes some exploratory analyses undertaken using a new model developed by the ERG.

5.2 Review of existing economic analyses

The company conducted a systematic review of studies of the cost effectiveness of metreleptin or other treatments for lipodystrophy, and studies of costs, resource use and HRQoL associated with lipodystrophy. The details of the search strategy were provided in the Section 17.3, Appendix 3, of the company submission.[1]

5.2.1 Searches

A single combined search strategy was used for all of these areas. Searches were carried out during February 2017 and up to 7 March 2017. Details of the search strategies were provided in Appendix 17.3 of the CS. The selection of databases searched was adequate (Ovid Medline and Medline in Process, EMBASE, and the Cochrane Library Databases) and all searches were clearly reported and reproducible, the database name, database date span, and date searched was provided for the majority of the searches. The service provider used to search the Cochrane Library was not provided. Section 17.3, Appendix 3 of the CS,[1] listed Econlit being searched, no Econlit strategy was provided but following the company clarified that this was a mistake and Econlit was not searched. A search of key International HTA websites and disease specific conference websites was also undertaken but more specific details of these searches were not provided in the CS (i.e. search terms, website details and results retrieved).

ERG comment:

- The search strategies were generally well constructed and contained a combination of subject heading index and free text terms. The majority of subject heading terms were unnecessarily exploded but this would not impact on results retrieved.
- A good range of economic, costs and HRQoL subject heading terms and keywords were used in the strategies but a specific filter was not referenced.
- There were some discrepancies in the translation of the strategies between databases, for example, animal limits included in the EMBASE strategy but not the Medline strategy. However, these were minor and no significant errors in translation that would result in studies being missed.

- The Cochrane Library search strategy was much simplified and only searched for the term lipodystrophy using word variations. The ERG feels it would have been better to search for the different terms for the condition individually.
- The grey literature searches (CS Appendix 17.3.5) in the company submission did not provide full details of the search terms used, the precise date of the searches or the number of records. The ERG cannot therefore comment on the robustness of these searches.

5.2.2 Review process and results

The company conducted a systematic review of studies of the cost effectiveness of metreleptin or other treatments for lipodystrophy. The details of the search strategy were provided in the Section 17.3, Appendix 3, of the company submission.[1]

The selection criteria used for the health economic evidence were reported in Table D31 of the company submission (CS, page 138).[1] A total of 2,109 publications were identified from the electronic searches. After removal of duplicates, 1,005 publications remained. After title and abstract screening, 1,083 publications were excluded as these were not of relevance to the research question. A total of 21 articles were assessed in full for further evaluation. Of these, 18 were excluded based on population (n=7), study type (n=5), date (n=5) and outcome (n=1). Manual searches of key international HTA websites and disease specific conference websites identified no additional papers. This left three papers for data extraction; two papers considering HIV-related lipoatrophy and one paper considering HIV-related lipodystrophy and lipoatrophy. The flow of studies through the identification and selection processes is depicted in Figure D23 of the CS (CS, page 140).[1]

None of the three studies identified were considered relevant to the economic evaluation of metreleptin. A summary of the key characteristics of each of the identified studies is provided in the CS (CS, Table D32, page 142).[1] Quality assessments for two of the three identified health economic studies, based on an adapted assessment criteria list from Drummond and Jefferson (1996),[81] are also provided in the CS (CS, Table D33, pages 143-148).[1]

The studies were deemed by the company to meet most of the criteria for a well-reported, high-quality economic evaluation, but the scope of all three studies was not considered to be relevant to the submission of the metreleptin owing to the population studied.

ERG comment:

The ERG identified some inconsistencies between the inclusion criteria used to select cost effectiveness studies and those used to select studies for the clinical effectiveness section of the CS. For instance, studies of HIV-related LD were included in the cost effectiveness review, but not in the clinical effectiveness sections of the CS. The company, in the response to the clarification letter, stated that metreleptin is not indicated for the HIV-related LD population. Although the FDA prescribing guidelines state that metreleptin is not indicated for the treatment of HIV-related lipodystrophy,[82] this is not clear from either the NICE scope,[27] or the regulatory information provided in the CS (CS, section 3.1, pages 25-26).[1]

Also, in the CS, quality assessments for only two of the three identified studies were provided. It was not clear to the ERG, why no quality assessment was provided for the remaining study.

The models identified from the review seem to mainly focus on the HIV-related disease attributes and their cost/QALY impacts (e.g. CD4+ T-Cell count), and therefore do not provide relevant information on LD related disease attributes. Thus, the ERG concurs that none of the studies are relevant to the economic evaluation of metreleptin.

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

The company's submission to NICE presents a model-based cost effectiveness analysis using QALYs as the main health outcome in the comparison of metreleptin versus standard of care (SoC) for the treatment of patients with lipodystrophy. The model considers the patient population from the NIH follow-up study are representative of the lipodystrophy patients in the UK. The lipodystrophy patients in the company base-case include the following subgroups, which fall under the expected licensed indication for metreleptin, described in the CS.[1]

- adults and children who are six years old or older, with congenital or acquired GL
- adults and children who are 12 years old or older, with familial or acquired PL, characterised by leptin level < 12 ng/ml with triglycerides > 500 mmol/l and/or HbA_{1c} > 8 %, while on standard therapy

The intervention, metreleptin, is a recombinant analogue of the human hormone leptin, administered through subcutaneous injection. The comparator, SoC for lipodystrophy is considered to be the standard clinical management without metreleptin, including lifestyle modifications such as diet and exercise, use of lipid lowering drugs, and medications for diabetes.

The analysis takes the perspective of the NHS in England but some of the potential costs (like day care costs) which may fall under Personal Social Services (PSS) appear not to have been included.

The model simulates the metreleptin-eligible patients (according to the expected licensed indication) in the NIH follow-up trial, with and without metreleptin and estimates cost and health consequences over a 60-year time horizon. The cycle length of the model is one year. The primary model outcomes are the estimated incremental QALY gain, the incremental costs and incremental cost effectiveness ratio (ICER) associated with the use of metreleptin compared to SoC. Costs and health outcomes are discounted at a rate of 3.5%.

For those patients receiving metreleptin, an annual treatment acquisition cost of £852,859 is used for all patients, assuming that the treatment is administered in 10 mg doses. Based on the anticipated availability of smaller vial sizes, the company assumed an annual treatment acquisition cost of £434,633. The company submitted a simple PAS discount of [redacted] on the list price to PASLU. The annual costs for SoC were assumed to be £3,000. Upon starting treatment with metreleptin, it is expected that patients will remain fully adherent on metreleptin for the

rest of their lives, unless they discontinue the treatment. The model assumes the observed discontinuation from the patient level data of NIH follow-up trial and once the data are unavailable, an annual discontinuation rate of 2.05% is assumed.

ERG comment:
The scope of the economic evaluation is generally in line with the NICE scope, and the deviations in the company's decision problem are discussed in Section 3.3 of the ERG report. The ERG assessed the adherence of the scope of the economic evaluation to the NICE reference case, which is shown in Table 23 below.

Table 23: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE	The scope of the economic analysis is generally in line with the scope developed by NICE, deviations already discussed in Section 3 of the ERG report.
Comparator	Therapies routinely used in the NHS, including technologies regarded as the current best practice	Standard of care (SoC) is considered the only comparator, it is the established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes).
Perspective on costs	NHS and PSS	NHS perspective was adopted.
Perspective on outcomes	All health effects on individuals.	Yes, patient health benefits are included in the model. Benefits to other afflicted individuals (e.g. caregivers) are not included in the model but discussed qualitatively in the submission
Type of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	No, lifetime horizon should have been considered, but the time horizon was chosen as 60 years, and not all patients were dead at the end of the time horizon.
Synthesis of evidence on outcomes	Based on a systematic review	Meta-analysis was not used, as there is no connected network and no RCT available. Some adjustment methods were used to obtain relative comparative clinical-effectiveness estimates for metreleptin vs. SoC from the non-randomized evidence obtained from separate studies.
Measure of health effects	QALYs and life years	Health outcomes are valued in terms of life years and QALYs gained.

Element of economic analysis	Reference case	ERG comment
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	The disutility values associated with disease attributes in the model were derived from a discrete choice experiment, within a sample that is argued to reflect the general population (1000 respondents). The valuation was based on some QALY estimation techniques in the literature (Bansback et al., 2012[83]; Viney et al., 2014[84])
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects.	Costs and outcomes were discounted at 3.5%.
Equity weighting	An additional weighting can be applied for incremental QALYs above 10 years.	No additional equity weighting is applied to QALY gains.

In terms of the population, it is not clear that the NIH follow-up study trial population (used as the baseline population in the cost effectiveness model) is representative of UK lipodystrophy patients (i.e. in terms of GL/PL, female/male, congenital/acquired ratios etc.). Only one UK patient was included in the NIH follow-up study. If the characteristics of the LD patients in the UK are expected to differ from the NIH follow-up study, these differences should be reflected in the cost effectiveness model, as well.

It is unclear to the ERG if the treatment eligibility criteria, for the expected licensed indication reported in the CS, is considered only once at baseline or at every consultation whilst the patient is on the medication. For instance, a PL patient might have a high HbA_{1c} value at baseline and therefore be eligible for the metreleptin treatment. However, during the course of the disease her HbA_{1c} value might decrease to a value that is below 8%. It is uncertain from the CS, if the metreleptin treatment would be stopped for this hypothetical patient or not.

In addition, the latest available information (09/03/2018) suggests that: [redacted]

The choice of the time horizon (60 years) seemed to be unsuitable, since at the end of the time horizon of the model, a substantial part of the population (e.g. 26.7% of the metreleptin arm)

was still alive. The time horizon and the mortality calculations should be adjusted in such a way that a negligible number of patients is alive at the end of the time horizon.

5.3.2 Model structure

The CS states that an Excel-based patient level Markov model was developed to perform the cost effectiveness analysis of metreleptin in GL/PL patients. In the CS, the justification of the modelling approach was provided using the taxonomy and the checklist given in Brennan et al. 2006[85] The model intends to simulate the disease progression of lipodystrophy, with and without metreleptin (i.e. SoC with metreleptin vs. SoC only), by using the patient level data from the NIH Follow-up study and GL/PL Natural History study. Patients are modelled for a maximum of 60 years from the start of the treatment. The health state of a patient is determined by the set of attributes listed below, which indicates the level of impairment due to the disease.

- Organ impairment related attributes
    - Heart, kidney, pancreas and liver abnormalities (list of conditions that would fall under an organ abnormality is given in Figure 34 of the CS)
- Lab related attributes
    - HbA_{1c} levels (partial/ no response), triglyceride (partial/ no response) levels
- Other attributes
    - Hyperphagia, ability to work/ perform at school, physical appearance, fast disease progression

In addition to the attributes above, hypoglycaemia events for each patient throughout his/her lifetime are also simulated in the model. The baseline values for these attributes at the start of the model are derived from the NIH follow-up study (including all 112 patients) for both metreleptin and SoC treatment arms.

For the metreleptin treatment arm, real-world data from the NIH follow-up study is used to populate the model for the attributes of heart, kidney, pancreas and liver impairment until the end of the data availability. Once real-world data are no longer available for a given patient, organ abnormality progression is extrapolated at an aggregate level (i.e. in terms of cumulative number of impaired organs), following a Markov process. For SoC, the cumulative number of impaired organs is extrapolated directly from the start of the time horizon, since the company stated that there were no patient level data on organ abnormality. The conditional organ-specific impairment probability weights are applied onto the extrapolated cumulative number of impaired organs to get an estimate for the organ-specific abnormality costs and disutilities accrued at a given period, when organ-specific impairment data are not available. The details of this extrapolation exercise for both the metreleptin and SoC arms (e.g. how the transition probabilities for the Markov process are derived from the NIH follow-up study for metreleptin and from the GL/PL natural history study for SoC) will be discussed in Sections 5.3.3.1 and 5.3.3.2.

For the blood lab attributes (i.e. HbA_{1c} and triglycerides), real-world data are used to populate the model for each patient, until data availability for the metreleptin arm. A last observed

carried forward (LOCF) approach is followed for extrapolating these attributes beyond data availability, until the end of the time horizon.

For the other attributes, in the NIH follow-up study, real world data seem to be recorded, at most, twice; one measure at baseline and a second measure a year (or more) later. The latter value for the attribute is applied from the first cycle and onwards for the patients receiving metreleptin.

For patients receiving SoC, for all attributes other than organ impairment related attributes, the baseline values from the NIH follow-up study are assumed to remain the same until the end of the time horizon.

Only age, cumulative number of impaired organs and type of the lipodystrophy (i.e. GL or PL) are assumed to have a direct impact on a patient's mortality, whereas all attributes listed above as well as the hypoglycaemia events are assumed to have a direct impact on a patient's QoL and costs.

In the base-case, the average of the model outcomes from the NIH follow-up study patients who fell within the original expected licensed indication reported in the CS (80 out of 112 patients) were presented. Similarly, in the subgroup analyses, the average of the model outcomes from those NIH Follow-up trial patients who were in the considered subgroup (e.g. for the PL subgroup, the average model outcomes from the 17 PL patients from the NIH Follow-up trial) were presented.

ERG comment:
The ERG agrees with the company that a patient level modelling approach would be more appropriate for the modelling of the course of the disease for lipodystrophy. However, it is not clear to what extent the potential additional advantages of a patient level modelling approach in comparison to Markov cohort approach were realised in the CS model.

Firstly, the first order stochastic uncertainty (i.e. random variability in outcomes between identical patients) was not explored in the CS model. Instead, each patient in the NIH follow-up study was modelled as an individual cohort, and the model outcomes of that patient were not taken into account if that patient did not fall with in the category for the analysed population (e.g. for expected licensed indication population, results from GL patients with baseline age smaller than 6 were not taken into account). No sampling procedures such as bootstrapping were employed. This modelling approach might underestimate the overall uncertainty of the course of the disease and might overemphasise the dependence on the assumption of the representativeness of the NIH follow-up study for LD patients. This might be problematic, since some of the subgroup results are based on the model outcomes from only a small number of patients (e.g. PL subgroup results depend on model outcomes from only 17 patients).

In the CS, the formal selection criteria for the attributes that are modelled for each patient were not clearly explained. Not all of the disease attributes identified in Section 17.6, Appendix 6, of the CS were included in the model (e.g. depression, neuropathy, amputation, retinopathy,

neutralising antibody risk etc.) It is not clear to the ERG how the final list of attributes included in the model were selected, furthermore it is unclear whether any other relevant and important attributes for lipodystrophy patients were not included in the model.

The current extrapolation approach used in the model for disease attributes ignores all possible interdependencies between disease attributes. All disease attributes are modelled/extrapolated independently of each other. The ERG considers this approach highly questionable, as in other metabolic disease models (e.g. diabetes) most disease attributes are interlinked, for instance the current value of an attribute is used as an input while estimating the future value of another attribute (e.g. cardiovascular disease risk in the next period might be associated with this period's HbA_{1c} and triglyceride levels).

Besides overlooking possible interdependencies in disease attribute extrapolation, the model also applied the extrapolation from different time points in the metreleptin and SoC arms. For patients in the metreleptin arm, the extrapolation of disease attributes is applied from the last observation point (of the available real-world data for each patient) onwards until the end of the time horizon. However, for the patients in the SoC arm, the extrapolation of disease attributes is always applied from the baseline (since there are no real-world data for SoC). This difference in the start times for the extrapolation in the model might lead to an underestimation of the uncertainty for the patients under metreleptin.

In the model, the cumulative number of organ impairments was considered as the primary disease progression surrogate. The ERG has serious concerns about this approach, which will be elaborated in the next section.

5.3.3 Evidence used to inform the company's model parameters

Table 24, below, presents a summary of the evidence sources used to inform the company's model parameters. A more detailed list of model parameter values and sources is presented in the CS (CS, Table D37, pages 162-163).

Table 24: Summary of evidence sources used to inform key parameter groups in the company's model

Parameter group	Source of parameter values
Initial patient distribution (disease attributes, age, sex, disease type)	Based on the baseline from the NIH Follow-up study, both for SoC and metreleptin arms.
Transition probabilities for the organ impairment (metreleptin)	The real-world data from the NIH Follow-up study is used to populate the model until data is available. When there is no real-world data available, disease progression (in terms of total number of organs impaired) is extrapolated by a Markov process, based on transition probabilities that are estimated from the transitions of the number of impaired organs in the whole population of the NIH Follow-up study.
Transition probabilities for the organ impairment (SoC)	From the start of the time horizon, disease progression (in terms of total number of organs impaired) is extrapolated by a Markov process, based on transition probabilities that are estimated by the transitions from a subset of the GL/PL Natural History study. The subset is

Parameter group	Source of parameter values
	selected based on a matching method to make the baseline characteristics of the two studies, NIH Follow-up study and the subset of the GL/PL Natural History study, similar (in terms of age, gender and the initial organ damage)
Transition probabilities for blood-lab attributes (HbA_{1c} and triglycerides)	For the metreleptin arm, the real-world data from the NIH Follow-up study is used directly, to populate the model until data is available. When the real-world data becomes unavailable, the LOCF method is used to extrapolate the blood-lab attributes and the last observed data is assumed for all the periods until the end of the time horizon. For the SoC arm, the baseline blood-lab attribute values from the NIH Follow-up study are assumed to remain unchanged throughout the whole time horizon.
Transition probabilities for other attributes (e.g. hyperphagia, ability to work/study, reproduction, physical appearance and fast progression)	In the metreleptin arm, for some of the patients, some of the disease attributes are assumed to improve from the baseline value. This improvement is assumed from the first cycle and onwards until the end of the time horizon. It is stated that these improvements were based on the observed patterns in the NIH Follow-up study. For the patients in the SoC arm, all these disease attributes are assumed to remain unchanged from their baseline values.
Adverse events (hypoglycaemia)	In the metreleptin arm, the real-world data from the NIH Follow-up study is used directly, to populate the model until data is available. When the real-world data becomes unavailable, the mean imputation method is used to extrapolate the number of hypoglycaemia events per year until the end of the time horizon. For the SoC arm, it is assumed that the patients do not experience hypoglycaemia events.
Treatment discontinuation	In the metreleptin arm, the patients are at risk of discontinuation from the metreleptin treatment. The observed treatment discontinuation data (i.e. the proportion of the time each patient is on metreleptin treatment in each period) from the NIH Follow-up study is used to populate the model until the data is available. A weighted overall average value of 2.047% for the discontinuation rate is applied to the patients who are still on the treatment at the last observation point, at each cycle until the end of the time horizon. The discontinuation from the metreleptin treatment has implications on the drug acquisition costs and organ impairment progression transition probabilities (for discontinued patients, related parameters from the SoC arm are applied).
Mortality	A Cox proportional hazard model is fitted to the GL/PL Natural History data, with number of impaired organs as the only independent, time-varying covariate. The resulting hazard ratio from this model represents the proportional change in the hazard rate due to an additional impaired organ.

Parameter group	Source of parameter values
	To derive the survival probabilities based on a given number of organ abnormalities, this hazard ratio is applied to: 1) for GL patients, to the survival curve fitted to the patient level survival data from the GL sub-population of the NIH Follow-up study; 2) for PL patients, to the gender/age adjusted mortality figures from the UK life table (based on the sex ratio in the PL sub-population of the NIH Follow-up study). Both the GL and PL curves above are adjusted based on the baseline number of average number of the impaired organs from the NIH Follow-up study data.
Utility decrements for the lipodystrophy complications	A discrete choice experiment (DCE) is used to provide an estimate of health disutilities for the key lipodystrophy attributes selected by the CS. An additive approach is followed while implementing the disease attribute disutilities simultaneously. Perfectly healthy individual was assumed to have a utility of 1.
Metreleptin treatment costs	Data on file from Aegerion.
Standard of care treatment cost	Assumption
Costs for lipodystrophy related complications and other resource use	KOL input and NHS reference costs.

5.3.3.1 Extrapolation of organ impairment progression

Abnormalities in four organs (heart, kidney, liver and pancreas) are considered in the model and the conditions that are categorised as organ abnormalities for each of the four organs are listed in Table 25 below.

Table 25: List of conditions that are categorised as organ abnormalities

Organ	Condition(s)
Liver	Ectopic fat deposit on liver Hepatomegaly Hepatic steatosis Steatohepatitis Cirrhosis Liver failure
Heart	Cardiomyopathy Heart failure Myocardial infarction Arrhythmia
Kidney	Chronic kidney disease Nephropathy Kidney failure
Pancreas	Pancreatitis
Source: Table 34 in the CS.[1]	

Organ impairment progression in the metreleptin arm

In the NIH follow-up study, real-world data pertaining to each patient's organ-specific abnormality were available for a limited time. When real-world data was no longer available,

for each patient the total number of abnormal organs was extrapolated using a Markov process. The progression probabilities (i.e. transition probability for developing the next organ impairment) were estimated by fitting exponential parametric survival functions to each of the four KM curves given in Figure 1, derived from the NIH follow-up study. The first KM curve in Figure 1 below represents time to develop the first organ abnormality; the second KM curve represents time to develop the second organ abnormality (given one abnormality at the baseline); the third KM curve represents time to develop the third organ abnormality (given two abnormalities at the baseline) and the last KM curve represents time to develop the fourth organ abnormality, given three abnormalities at the baseline.

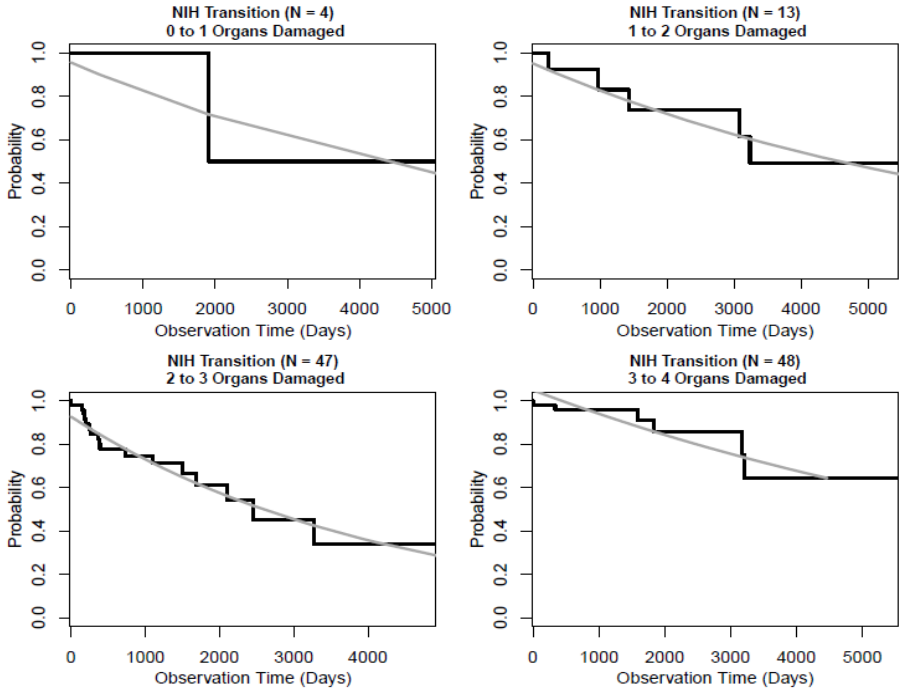
The KM and the fitted exponential curves for disease progression from the NIH follow-up study and the resulting progression probabilities obtained from the fitted exponential curves are given in Figure 1 and Table 26, respectively.

Table 26: Estimated annual progression probabilities from the NIH follow-up data (N=112*)

Progression event	Estimated progression probability	Number of patients at risk	Number of progressions
0 to 1	5.4%	4	1
1 to 2	5.0%	13	5
2 to 3	8.3%	47	17
3 to 4	3.9%	48	7

Source: Table 70 in the CS.[1]
*NIH follow-up study included 114 patients, but sufficient data after baseline is available for only for 112

Figure 1: NIH follow-up study organ abnormality progression



Source: Figure 1 in the second response to the CL.[39]

Organ impairment progression for SoC in the unmatched cohort

The same extrapolation approach (Markov process for the total number of abnormal organs) is followed for organ impairment progression under SoC. The estimated transition probabilities that are derived from the GL/PL natural history study data are applied to patients from baseline until the end of the time horizon. Note that at baseline, the patients are assumed as identical in both the SoC and metreleptin arms in the electronic model. However, if the extrapolated number of impaired organs of a SoC patient led to fewer impaired organs than for that patient on metreleptin (this can happen since real-world data are being used in the metreleptin arm), then the extrapolated number of impaired organs in the SoC arm was replaced by that from the metreleptin arm.

The KM and the fitted exponential curves for disease progression from the GL/PL natural history study and the resulting progression probabilities are given in Section 17.6.2.1, Appendix 6, of the CS (CS, Figure 35 and Table 70, pages 256-257).[1] Note that these probabilities are from the original, "unmatched" population of the GL/PL natural history study, and they are not used in the model. The matching exercise and the consequential "matched" transition probabilities will be explained further in Section 5.3.3.3.

ERG comment:

The ERG has several concerns surrounding the modelling of the disease progression in terms of the number of organ abnormalities, the categorisation of the clinical conditions to organ abnormality types (and resolving of the organ impairment in the metreleptin arm), the data updates in the evidence submitted by the company after the CS, differences between the NIH follow-up study and GL/PL natural history studies, and some other methodological concerns

regarding the estimation of the transition probabilities related to organ impairment. These issues are listed, in summary, below:

1. Level of aggregation while modelling the impacts of the lipodystrophy progression on different organs
2. Difficulties in the interpretation of the real-world data on the organ impairments provided in the CS
3. Data updates delivered after the original CS
4. Differences between the NIH follow-up study and GL/PL natural history study in terms of participant baseline characteristics and inherent structural censoring (patients were observed from their enrolment time and onwards in the NIH follow-up trial, whereas in the GL/PL natural history study, the retrospective patient records were collected to the earliest possible time point)
5. Staggering method (i.e. assuming one day in between two or more organ impairments that were observed simultaneously)
6. Lack of clarity regarding the approach of the incorporation of the time to event data from the NIH follow-up study and from the GL/PL natural history study
7. A patient's simulated number of impaired organs under SoC is forced to be higher than that patient's simulated number of impaired organs under metreleptin in each cycle
8. Lack of details and justification for the methods followed and the assumptions taken while estimating the transition probabilities for the number of organs impaired:
    a. The statistical modelling of the organ impairment process is not in line with the observed organ impairment progression from the real-world data
    b. The current approach implicitly assumes that the organ impairment process possesses the Markov memoryless property
    c. Patient characteristics have no impact on the transition probabilities for the number of impaired organs.
    d. The plausibility of the selected method used in the company submission for the estimation of the transition probabilities from longitudinal data.

<u>Level of aggregation while modelling the impacts of lipodystrophy progression on different organs</u>

In the extrapolation of organ impairment progression, only the cumulative number of organ impairments (out of four organs) was taken into account, based on a non-transparent categorisation applied to the clinical conditions identified from the real-world data that were collected/recorded in an ad-hoc manner. It is not clear why the type of affected organ (pancreas, kidney, heart and liver) and the severity of an organ abnormality (e.g. ectopic fat deposit on an organ or an organ failure) were not taken into consideration in the analysis. Based on this assumption in the CS, the cost and health outcomes from an ectopic fat deposit around the liver are assumed the same as those from a myocardial infarction or those from a kidney failure. Furthermore, if a patient has two conditions affecting the same organ (e.g. heart failure and myocardial infarction), the cost and QALY impacts of the second condition affecting the same organ would be ignored. These implications were deemed to be highly unrealistic and unjustifiable by the ERG.

The company, in its response to the clarification letter, provided three arguments to justify this high aggregation level for organ impairment. These arguments were 1) evidence from other cost effectiveness models in the literature which have very simple model structures 2) traceability of the cost effectiveness model from the CS and 3) data constraints.[39]

The ERG disagrees with the first argument, related to evidence from other cost effectiveness models in the literature, as the provided examples were in other, unrelated disease indications (e.g. late stage oncology or aortic aneurysm surgery). With respect to the traceability concern, the ERG considers that this cannot be a justification argument, since this issue would be resolved with transparent programming and reporting practices. Finally, the ERG can understand the company's argument on data constraints; if additional states were considered for the type and severity of organ impairment, the data from the NIH follow-up trial and the GL/PL natural history study might be insufficient to populate the necessary transition probabilities between the additional states. However, the ERG considers that there may be alternative options to incorporate organ impairment severity/type, other than incorporating additional states; for instance, a clinically plausible cumulative organ impairment severity index could have been developed and incorporated as a time-dependent disease attribute in the simulation. Using this approach, the difference in severity among patients having the same number of organ impairments could have been partially reflected (e.g. the cumulative organ impairment severity index of a patient having arrhythmia and ectopic fat deposit around liver would be lower than a patient having myocardial infarction and kidney failure).

Difficulties in the interpretation of the real-world data on the organ impairments provided in the CS

The ERG had considerable difficulties in tracing and interpreting the real-world organ impairment data provided. The ERG had the impression that the conditions which are categorised as an organ impairment in Table 25 above were considered to be permanent, non-reversible conditions; this was how organ impairment was extrapolated in the model, as the number of impaired organs can only stay the same or increase over time. However, from the real-world data provided in the electronic model of the CS, it became clear to the ERG that these conditions could actually be reversible (i.e. in some of the cycles, the previously existent abnormalities of the kidney, pancreas and liver had resolved). When asked about these improvements, the company gave more details in its response to the clarification letter:

"Improvement in kidney and liver abnormalities were assigned to patients with proteinuria (kidney) or impaired hepatic function (liver) based on a reduction of at least 20% of previously abnormal laboratory readings for protein excretion (kidney) and ALT/AST (liver) in the year after metreleptin treatment (…)

As laboratory data for protein excretion and ALT/AST were not available as a time series in the natural history data, we chose to only track the development of organ abnormalities and not subsequent resolution in the organ progression and survival analysis (…)

The only type of pancreatic abnormality included in either the organ progression / survival analysis or the CE model was pancreatitis. An NIH nurse reviewed patient records for evidence

of pancreatitis prior to metreleptin initiation and identified which patients experience no re-occurrence of pancreatitis after metreleptin initiation." (Response to clarification letter, page 27)).[39]

Considering organ impairment improvements only for the metreleptin patients and not for the patients on SoC may well lead to a bias in favour of the metreleptin. Also, whilst the ERG acknowledges that an improvement in a blood-lab value might be an indicator of improvement in organ function, we do not agree that an arbitrary level of improvement in blood-lab values can automatically be considered to be synonymous with the resolution of an impairment. Within the given time constraints, the ERG cannot audit whether or not the categorisation of organ impairment conditions was conducted consistently. Hence, the ERG cannot judge the reliability of the real-world data used in the estimation of the clinical input parameters.

Data updates delivered after the original CS

The company updated the real-world data on organ abnormalities, used in the statistical analyses, twice following the original submission. In its first response to the clarification letter, the company stated that "…, data for the NIH Study were updated upon further validation. Specifically, one patient for whom the latest survival status was uncertain is now confirmed to be alive. Moreover, the end of study period has been updated from January 22, 2017 to December 18, 2017. Pancreatitis data have also been updated to reflect validation of pancreatitis incidence by an NIH clinician. We also corrected an inconsistency in which heart conditions were considered abnormalities in the NIH data used for this analysis relative to the definition used in the Natural history data and the definition used in the CE model. Specifically, hypertension was included as an abnormality in the previous version of this analysis. The revised data is consistent with the definition of heart abnormality used in the CE model." (Response to clarification letter, page 57).[39]

In its second response to the clarification letter, the company stated: "We have additionally corrected some inconsistencies in the definition of organ abnormalities between the NIH Follow-Up Study and Natural History Study and have excluded patients with certain missing data prior to treatment from organ abnormality progression and survival analyses.", and in the footnote mentioned that: "corrections to the NIH Follow-Up Study data are described in the NIH Follow-Up Study summary report. Additionally, this analysis was previously completed using an older version of pancreatitis data for NIH patients and now uses the current, validated version (consistent with other analyses and the data used for the CE model)." (Response to clarification letter, page 21).[39]

Since these data updates appear to have been conducted in an *ad-hoc* manner, i.e. the recording of the organ abnormalities and its categorisation was not specified in a pre-determined protocol and the changes were not transparent, the ERG cannot audit the provided real-world data on organ abnormalities and cannot judge the reliability of these data.

The impact of these data updates on the transition probabilities used in the electronic model will be explained in Section 5.3.4.

Differences between the NIH follow-up trial and GL/PL natural history study

The company noted that the patients from the GL/PL natural history study have data from birth, whereas for patients in the NIH follow-up study, data are only available from the start of their treatment. The company also noted that the resulting truncated data from the NIH follow-up study may lead to biased estimates. Upon a request for clarification on this expected bias, the company provided the following argument in its response to the clarification letter: "Patients with truncated histories are more likely to transition once they are observed than those patients whose prior histories are fully observed. This is because patients with truncated histories are likely to have already spent some time in the state in which they are first observed. Patients whose entire history is observed, on the other hand, spend a longer amount of time in the observed state before transitioning even if they transition at the same rate. This implies that we would estimate higher transition probabilities for those patients with truncated data (NIH patients) than those with full data (GL/PL patients)".(Response to clarification letter, page36).[39]

The ERG considers that the potential bias resulting from this asymmetry of truncation can be partially corrected by statistical matching methods. Furthermore, this argument of bias from the company conflicts with the company's current modelling approach that is built on the "memoryless" assumption, which presumes that a transition from one state to another does not depend on the time spent in the former state. This assumption will be further discussed in point 7b.

"Staggering" method applied to the multiple organ impairments diagnosed in the same visit

The ERG requested an explanation for the steep declines observed in the KM curves near t=0, in all sub-figures depicted in Figure 35 of the CS (CS, Section 17.6.2.1, Appendix 6, page 256).[1] In its response to the clarification letter, the company stated that the information on organ abnormalities was collected during patients' physician visits, and that sometimes patients were diagnosed with abnormalities to multiple organs at the same visit.

The company stated that they dealt with these simultaneous multiple organ diagnoses by "staggering" the diagnoses so that they are one day apart from each other. This resulted in the current KM curves, where some patients seem to spend only one day in an abnormality state before transitioning to the next.

The company provided the "staggered" number of instances in which patients in the NIH follow-up and GL/PL natural history studies were diagnosed with abnormalities to multiple organs on the same visit, as reflected on the transition KM curves:

"-18 natural history patients develop abnormalities to two organs after having had no prior abnormalities
-12 natural history patients and 1 NIH patient develop abnormalities to two organs when they already have one afflicted organ
-10 natural history patients and 1 NIH patient develop abnormalities to two organs when they already have two other afflicted organs

-4 natural history patients and 2 NIH patients develop abnormalities to 3 organs after having had no prior abnormalities
-2 natural history patients and 1 NIH patient develop abnormalities to 3 organs when they have previously had one afflicted organ
-1 natural history patient develops abnormalities to all four organs at the same time" (Response to clarification letter, page 38)[39]

This "staggering" approach would overestimate the speed of progression of the organ abnormality and, since it was applied primarily in the GL/PL natural history study records, this overestimation affected mostly the speed of organ impairment progression probabilities in the SoC arm. Therefore, the ERG anticipates the actual transition probabilities for organ impairment progression in the SoC arm to be smaller than the estimates provided in the CS. However, the ERG cannot quantify this, given the time limitations, and given that the data and the statistical codes provided by the company were not transparent and clear.

Lack of clarity regarding the approach to the incorporation of the time to event data from the NIH follow-up study and from the GL/PL natural history study
In the CS, while generating the KM curves from the "*time to next organ impairment*" data from the NIH follow-up and GL/PL natural history studies, it was not clear whether a death event was considered as a censor or an organ impairment event.

In their first response to the clarification letter, the company provided some results (Table 4 to Table 7 in the first tier of the response to the clarification letter, page 32-34), where the impact of death event categorisation was explored in *de novo* Cox proportional hazard model analyses conducted on several pooled datasets of NIH follow-up and GL/PL natural history studies (original pooled datasets, original matched pooled datasets, updated pooled datasets and updated and matched pooled datasets).[39] From these results, it can be seen that the categorisation of the death event (as an organ impairment event or as a censoring event) has a considerable impact on the hazard ratios (hazard rate for the organ impairment under metreleptin vs. under SoC); considering the death event as a censoring event seems to decrease the hazard ratios. The company did not explain the reasons for this effect of censoring in detail and more importantly, the company did not state which categorisation approach was chosen in the analyses that yielded the organ progression transition probabilities that were used in the electronic model.

Furthermore, the ERG has doubts about the compatibility of the time to event data used for the NIH Follow-up study and for the GL/PL Natural History study.

In Figure 36 from the CS (CS, Section 17.6.2.1, Appendix 6, page 257), the numbers at the top of each subfigure (N=4 for 0 to 1 organ damaged, N=13 for 1 to 2 organs damaged, N=47 for 2 to 3 organs damaged, N=48 for 3 to 4 organs damaged) sum to 112, which is the total number of patients in the NIH Follow-up study.[1] This suggests that the Kaplan-Meier (KM curves) in Figure 36, were incorrectly based on time-to-event data that were not contingent on number of organs already damaged, i.e. not all of the patients who developed the n^{th} organ impairment were considered in the next KM curve, which is analysing the time to develop the $(n+1)^{th}$ organ

impairment. For example, it seems highly unlikely that no one who progressed from 0 to 1 subsequently progressed from 1 to 2 organs damaged and that no one who progressed from 1 at the start to 2 subsequently progressed from 2 to 3 organs damaged. This implies that the rate of progression has mostly likely been underestimated.

The company seems to follow a different approach when analysing the time to next organ impairment from the GL/PL Natural History study. In Figure 35 from the CS (CS, Section 17.6.2.1, Appendix 6, page 256), the numbers at the top of each subfigure (N=142 for 0 to 1 organ damaged, N=151 for 1 to 2 organs damaged, N=120 for 2 to 3 organs damaged, N=77 for 3 to 4 organs damaged) sum to 490, which is larger than the total number of patients in the GL/PL Natural History study (N=178).[1] This suggests that the KM curves in Figure 35, were based on time-to-event data contingent on number of organs already failed, i.e. all of the patients who developed the n^{th} organ impairment were taken into account in the baseline number at risk of the next KM curve, which is analysing the time to develop the $(n+1)^{th}$ organ impairment. This is confirmed by Figure 4 of the short report of on the GL/PL Natural History study supplied in response to the clarification letter.[40]

Overall, the approaches used in the incorporation of the time to event data from the NIH Follow-up study and from the GL/PL Natural History study appear to be incompatible. This would cause a bias, which favours metreleptin. However, the data and the codes provided by the company regarding the NIH Follow-up study were not transparent and therefore the ERG cannot scrutinise them adequately.

A patient's simulated number of impaired organs under SoC is forced to be higher than that patient's simulated number of impaired organs under metreleptin in each cycle

In the electronic model, there is a logical formula that forces the simulated number of impaired organs of a patient under the SoC to be always larger than or equal to the simulated number of impaired organs of that patient under metreleptin.

Even though the organ impairment transition probabilities are higher for SoC, sometimes the extrapolation under the SoC arm can result in fewer organs being impaired compared to the metreleptin arm, since in the metreleptin arm, real-world data is used as an input until the data stops being available. In the instances, where the number of organ impairments of a patient under SoC is lower compared to the same patient in the metreleptin arm, the logical formula takes the higher number from the metreleptin arm to use for SoC.

The ERG deems the use of this formula to be problematic, since it creates a bias favouring metreleptin. The treatment effect and the potential benefit of metreleptin was already reflected in the transition probability estimations. Adding a formula that forbids the simulated number of impaired organs of a patient under the SoC from being smaller than the simulated number of impaired organs of that patient under metreleptin, cannot be considered as an evidence-based modelling practice, but is rather a reflection of the company's expectation bias in the electronic model. In Section 6, the impact of relaxing this programming constraint on the cost effectiveness results will be presented in the exploratory analyses.

The statistical modelling of the organ impairment process is not in line with the observed organ impairment progression from the real-world data

In the statistical modelling approach of the organ impairment process, it was assumed that the cumulative number of impaired organs can stay the same or increase by one. The observations from the real-world data were not in line with this assumption. As discussed previously, in the NIH follow-up study, it was observed that sometimes organ abnormalities resolved over time. Also, from the real-world data it was sometimes observed that multiple organ impairments developed in a given year.

The company, in its first response to the clarification letter, argued that the simplification of allowing only one organ impairment in a year would result in a conservative estimate of the benefit of metreleptin treatment, because with metreleptin, patients would experience multiple organ impairments less frequently. The ERG considers this deduction as speculative, without any formal analysis.

The current approach implicitly assumes that the organ impairment process possesses the Markov memoryless property

The statistical approach the company followed assumed that the probability distribution for the total number of impaired organs would possess Markov memoryless property (e.g. transition from one state to another does not depend on the time spent in the former state). The ERG asked the company to justify the plausibility of this assumption.

In its first response to the clarification letter, in Table 8 (Response to clarification letter, page 38), the company provided the results of the linear regression models conducted on the matched GL/PL Natural History cohort data, where the time to develop the n^{th} organ impairment was the dependent variable, and the time spent with *(n-1)* organ impairment was the only independent variable for *n=1,2,3* and *4*.[39] The company interpreted the results as indicating that there is no strong evidence for a consistent, significant correlation between time spent in the former state and time to progression, for the matched control patients from the GL/PL natural history study. This test was not conducted for NIH follow-up study, since the patients in this study were not followed from their birth.

The ERG considers that there could be other available tests for the Markov memoryless property, however the ERG also considers that the memoryless assumption is not the assumption that is driving the final results that affect decision making.

Patient characteristics have no impact on the transition probabilities for the number of impaired organs

The current modelling approach implicitly assumes that patient characteristics, such as age, gender, type of lipodystrophy, type of organ impairment and its severity, time on metreleptin treatment, blood glucose/triglyceride levels have no impact on the transition probabilities for the number of impaired organs.

In its first response to the clarification letter (Response to clarification letter, question B3.e3, pages 40-43), the company presented the results of some adjusted Cox proportional models,

where the treatment, type of lipodystrophy, gender, baseline age and type of organ impairment at baseline were added as covariates, applied on the pooled dataset of NIH follow-up study and matched GL/PL natural history study population. These results indicated that, when the covariates were adjusted, the treatment seemed not to have a significant impact on the estimated time to next organ impairment, whereas other baseline patient characteristics, such as the baseline organ impairment type seemed to have a substantial impact, even though the direction of the impact was not always consistent and in line with the *a priori* expectations of the ERG (sometimes positive and sometimes negative).[39]

The company acknowledged that these characteristics were important contributors to survival and progression. However, they stated that they did not anticipate that using the estimated transition probabilities in the original CE model would be biased by systematic differences in these attributes across groups, as the goal of the matching was to balance several of these attributes across the NIH (treated) patients and natural history study (control) patients.

The ERG does not agree with the company's anticipation that there would not be any bias by not including these patient characteristics in the statistical analysis of organ impairment, because of the matching between the NIH follow-up study and the GL/PL natural history study populations. Firstly, the matching exercise conducted by the company took only age, gender, type of lipodystrophy and the initial number of organ impairments into account. Secondly, without the data on the baseline organ impairment type of the matched populations from the two studies, the size and the direction of the potential bias arising from not incorporating these covariates cannot be known.

<u>The plausibility of the selected method used, in the company submission, for the estimation of the transition probabilities from longitudinal data</u>

Due to the issues discussed above, the ERG had doubts about the appropriateness of the statistical approach selected by the company, especially given the fact that other standard methods for estimating Markov chain transition probabilities (e.g. multi-state models or maximum likelihood estimation methods) are existent in the literature and are commonly used.[86, 87]

Therefore, the ERG asked the company to conduct a *de novo* statistical analysis for the estimation and the extrapolation of organ abnormality progression, using commonly accepted methods, on the pooled dataset (including label-eligible patients from both NIH follow-up study as well as the natural history study), including all the relevant covariates. The company stated that they could not complete this request given the timelines. The ERG therefore cannot assess the direction and the size of the potential bias caused by not following standard statistical methods, as opposed to the approach followed by the company, whose major flaws are described above.

5.3.3.2 Derivation of mortality inputs for the model

Real-world survival data from the NIH follow-up study are used to populate the model for the survival of the metreleptin arm patients as long as there are data available. Beyond the follow-up period, each patient's survival is extrapolated using the corresponding fitted survival

distribution, depending on that patient's lipodystrophy type (i.e. PL or GL), adjusted according to the total number of organ abnormalities. For patients receiving only SoC, as there are no real-world data available, survival is extrapolated using the fitted distributions directly from the baseline.

Extrapolation of the survival of the GL patients

To provide mortality inputs for the GL patients in the model, the KM curve pertaining to the GL patients from the NIH follow-up study is extrapolated beyond the end of available data. The company declared that the approach described in Latimer et al. 2013[88] and Williams et al. 2017[89] is followed, while selecting the most appropriate fitted parametric curves (exponential, Weibull, lognormal and log-logistic) to the available KM data. The company considered that the exponential distribution would be the best fit based on the statistical fit (AIC) and visual inspection, which are depicted in Figure 38 and in Table 72 in the CS (CS, Section 17.6.2.2, Appendix 6, page 260).[1] The final baseline GL survival curve in the electronic model used the observed survival probabilities for years 0 to 16, and afterwards extrapolated survival probabilities from the exponential distribution.

Extrapolation of the survival of the PL patients

The company stated that there is no excess mortality due to PL, as these patients experience milder symptoms compared to GL patients, and the observed deaths in the NIH Follow-up study among PL patients were extremely low (only one death). Hence, the survival of the PL patients was extrapolated using the age and gender specific mortality figures from the latest (2014-2016) UK lifetables. The final baseline survival curve (based on the female to male ratio and average baseline age from the PL patient subgroup of the NIH Follow-up study) is presented in Figure 39 of the CS (CS, Section17.6.2.2, Appendix 6, page 261).[1]

Relationship between the organ abnormality progression and mortality

In the CS, it is assumed that the survival in a period is determined by the type of lipodystrophy and the number of organs impaired in that period. Other attributes such as the type(s) of organ impairment(s) or the length of time spent with a given organ impairment are assumed to have no impact on mortality.

The assumed relationship between mortality and the number of impaired organs was tested with a Cox proportional hazards model fitted to the GL/PL natural history study data. The number of impaired organs as a time-varying covariate is included in the Cox proportional hazards models to predict mortality for the full GL/PL population, GL subpopulation and PL subpopulation. The regression coefficients from these analyses for the full, GL and PL samples are given in Table 27 below.

Table 27: Cox proportional hazards model on GL/PL natural history study with number of impaired organs as time-varying covariate

Independent Variable	Regression Coefficient (Beta)	Exponential of Regression Coefficient (Hazard Ratio)	Standard Error	p-value
FULL SAMPLE				
Number of Impaired Organs	1.2839*	3.6108	0.3329	0.000115
GL SAMPLE				
Number of Impaired Organs	1.0897*	2.9734	0.4155	0.00873
PL SAMPLE				
Number of Impaired Organs	1.5237*	4.5892	0.5302	0.00406

Source: Table 73 in the CS.[1]
*Statistically significant at 1%

The company used Schoenfeld residual tests for the proportional hazards assumption for the number of impaired organs for the GL subpopulation, PL subpopulation and the whole patient population from the GL/PL natural history study. Results of these tests are provided in Table 74 of the CS (CS, Section 17.6.2.3, Appendix 6, page 264),[1] which suggested that there is insufficient statistical evidence to reject the null hypothesis that the slope of the residuals in time is approximately 0; this is interpreted by the company as indicating that there is no statistically significant correlation between time and the Schoenfeld residuals.

The company provided some alternative proportional hazards models fitted to the GL/PL natural history study data, by including additional covariates in the baseline model such as the gender, country of origin, age and lab values (HbA_{1c}, triglycerides and leptin levels). The results of the additional models are provided in Table 75 of the CS (CS, Section 17.6.2.3, Appendix 6, pages 265-267).[1]

Model 1 included squared and cubed versions of the main independent variable, number of impaired organs, to test for non-linear effects. Model 2 included additional demographic covariates such as age, gender and country of origin. Model 3 included additional blood-lab covariates such as HbA_{1c}, triglycerides and leptin. Model 4 included both blood-lab values and demographic values as additional covariates, both in the GL subpopulation, PL subpopulation and the whole patient population of the GL/PL natural history study. In all of these models, except for Model 1, the number of impaired organs was the only significant covariate.

Eventually the company chose to use the Cox proportional hazard model with the number of impaired organs as the only independent variable. The formal goodness of fit test results were

not provided and the reasons for the selection of the model to use in the base-case were not explained.

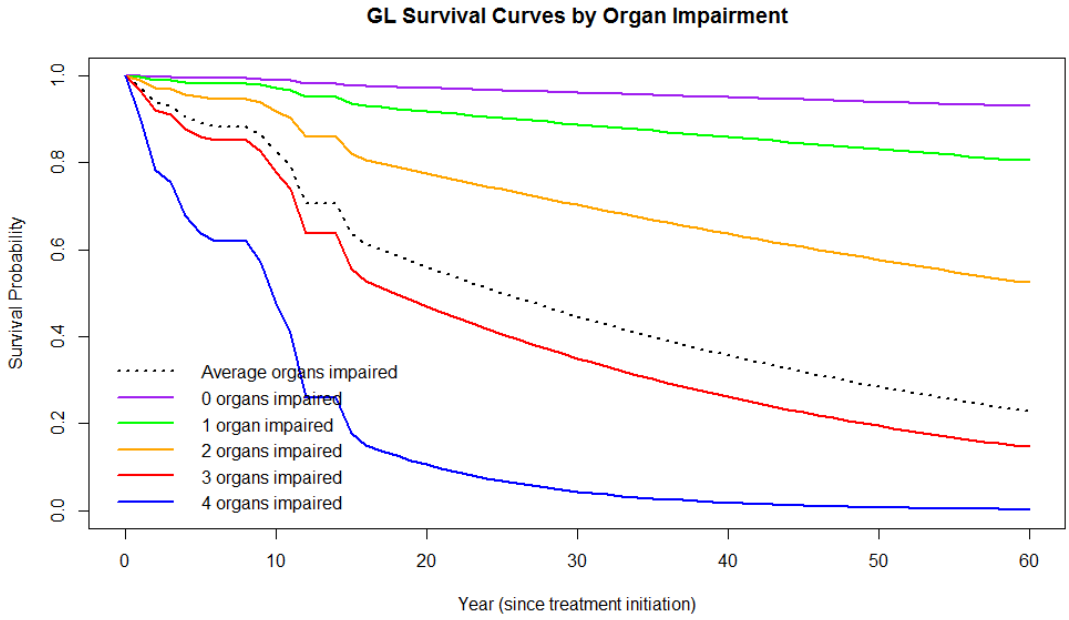
Organ abnormality specific survival curves

The company generated survival curves conditional on the number of organ impairments for the GL and PL patients, to use in the survival extrapolation in the electronic model. To construct these survival curves, baseline GL and PL survival curves obtained from the NIH follow-up data and from the UK population life table respectively were scaled by the coefficient obtained from the Cox model, whose results are given in Table 27 above.

The GL baseline survival curve was interpreted as the survival of patients with the average number of impaired organs among GL patients in the NIH follow-up study. Similarly, the PL baseline survival curve was interpreted as the survival of patients with the average number of impaired organs among PL patients in the NIH follow-up study.

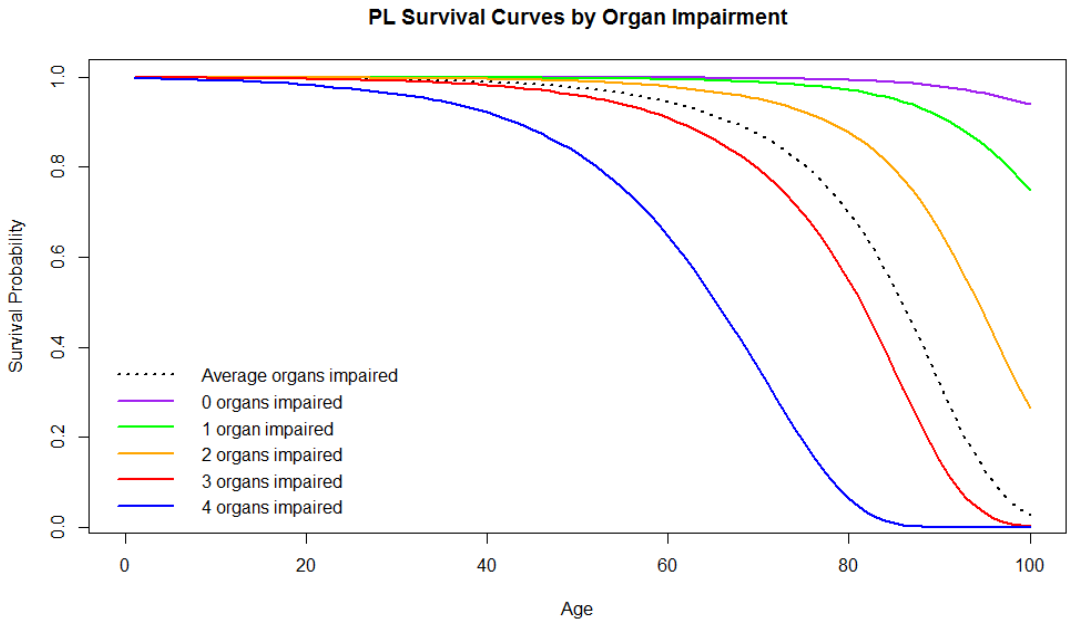
For both GL and PL patients, first the survival curves for the patients with 0 impaired organs were derived; then the survival curves with 0 impaired organs were scaled, by the Cox model coefficient, to derive the survival curves for patients with 1, 2, 3, and 4 impaired organs. This yielded five survival curves for the GL population and five survival curves for the PL population. Each curve corresponding to each of the possible levels of organ impairment (e.g. 0, 1, 2, 3, and 4). These curves for the GL and PL patients are shown in Figure 2 and Figure 3 below, respectively.

Figure 2: GL survival curves by organ impairment levels



Source: Figure 40 in the CS.[1]

Figure 3: PL survival curves by organ impairment levels



Source: Figure 41 in the CS.[1]

ERG comment:

The ERG has several concerns regarding the survival analyses conducted by the company and how the results from these analyses were implemented in the electronic model. The main issues are listed below:

1. Data updates delivered after the original CS
2. Estimation of the survival components from different datasets and synthesising the survival analysis results in a non-systematic manner
3. Lack of face validity for the GL/PL patient's survival extrapolation results (some GL/PL patients have a more favourable life expectancy than the general UK population)
4. Having a substantial number of patients alive (above 25%) at the end of the time horizon
5. Not checking the clinical plausibility of the GL survival extrapolation.
6. The assumption that survival is affected only by age, gender, type of lipodystrophy and number of organs impaired.
7. Wrong derivation of the conditional survival curves given a fixed number of organ impairments.

<u>Data updates delivered after the original CS</u>

As described in Section 5.3.3.1, the data used in the statistical analyses were updated twice after the company submission. Similar to the organ abnormality data, survival data from the NIH follow-up data were also updated. The ERG cannot audit these changes within the time available.

Estimation of the survival components from different datasets and synthesising the survival analysis results in a non-systematic manner

The survival analyses reported in Section 17, Appendix 6 of the CS included an extrapolation exercise (Section 17.6.2.2 of the CS) for the survival of the GL/PL patients using parametric models and national life tables, followed by an estimation exercise (Section 17.6.2.3 of the CS) for the relationship between organ abnormality and mortality.[1] While the extrapolation exercise was conducted on the patients from the NIH follow-up study, the estimation exercise was conducted on the patients from the GL/PL natural history study. The hazard ratio coefficient from the estimation exercise is applied to the parametric/life table survival curves obtained from the extrapolation exercise.

The ERG considers that for the sake of consistency, the estimation and extrapolation exercises should have been conducted on the same dataset and requested clarification from the company regarding the rationale of their approach.

The company stated that the estimation of the relationship between organ impairment and mortality was conducted using only the GL/PL natural history study because of the data limitations of the NIH follow-up study. They noted that, in the NIH follow-up study, information about the early stage of patients' disease was lacking and the observation window in the study was much shorter compared to the GL/PL natural history study. Nevertheless, the company provided the results of the same Cox proportional hazards model to estimate the effect of number of organ impairments on mortality, but using only NIH follow-up study in Table 9 (response to clarification letter, page 48) in their first response to the clarification letter.[39] The company dismissed these results as they were not statistically significant, and the estimated HRs for the GL population from the NIH follow-up study was lower compared to that from the GL/PL natural history study in Table 27 above (NIH follow-up: 1.46 for GL, 4.60 for PL population; GL/PL natural history: 2.97 for GL, 4.59 for PL population).

In addition, the ERG asked the company to provide the results from a *de novo* extrapolation and estimation exercise, using data from a pooled dataset including label-eligible patients from both NIH follow-up and natural history studies, incorporating the study ID as a separate covariate.

The company, in its first response to the clarification letter, stated that a time varying Cox proportional hazard model relating mortality to number of organs with abnormalities (as well as additional covariates) on pooled data was conducted.[39] First, a Cox proportional hazard model was run on the pooled dataset with all NIH follow-up study patients along with matched GL/PL natural history patients, based on the Mahalanobis matching method, using the latest available data. In the second analysis, all NIH follow-up study and GL/PL natural history study patients were combined.

The results of these analyses were presented in the company's first response to the clarification letter (Response to clarification letter, question B10.b, pages 49-53).[39]

In these analyses, conducted on pooled datasets of the GL patients, both the number of organs impaired and the patient's age at the start of the observation were significant covariates. For the GL patients, the HR for the number of impaired organs from these covariate-adjusted analyses on the pooled datasets (HR=1.99 when matched GL/PL natural history study population is used and HR=2.21 when all patients from the GL/PL natural history patients are incorporated) were between the HR obtained from NIH follow-up study only and the HR obtained from the GL/PL natural history study only.

In these analyses conducted on pooled datasets of the PL patients, the number of organs impaired was the only significant covariate. For the PL patients, the HR for the number of impaired organs from these covariate-adjusted analyses on the pooled datasets (HR=6.77 when matched GL/PL natural history study population is used and HR=5.25 when all patients from the GL/PL natural history patients are incorporated) were higher than the HRs obtained from the NIH follow-up study only and the GL/PL natural history study only.

The ERG has difficulty in interpreting these results as they are based on multiple changes implemented at the same time (i.e. covariate adjustment and combining data from both trials as well as the survival data update due to the latest follow-up). The company stated that these *de novo* survival analyses had been implemented in the economic model, and reported some ICER results, however the ERG cannot judge the correctness of the implementation, since hardcoded numbers were used in the implementation of the *de novo* survival models, and the values cannot be traced back to the results of the *de novo* statistical analyses.

Lack of face validity for the GL/PL patient's survival extrapolation results (some GL/PL patients have a more favourable life expectancy than the general UK population)

The ERG considers that some of the survival estimates in the submission lack face validity. For instance, in the model, PL patients who have zero or one impaired organ at baseline have a better life expectancy than the UK general population. Therefore, the ERG asked the company to provide alternative clinically plausible mortality estimates, which cannot be lower than the UK general mortality figures, even if the patient has no organ abnormality.

The company confirmed that the mortality estimates used in the original submission were not clinically plausible and implemented a cap for the survival estimates used in the electronic model that was attached to its response to the clarification letter. In the updated version, the model uses the annual survival probability from the UK life table if the survival probability estimates based on the analyses on the NIH follow-up and the GL/PL natural history studies were more favourable.[39] The ERG considers that this solution is an artificial one. Ideally, the company should have explored the reasons underlying the quite high survival outcomes from the model and should have chosen a plausible survival extrapolation that would not lead to implausible mortality estimates.

Having a substantial number of patients alive (above 25%) at the end of the time horizon

In the company's original model, the '*percentage of people alive*' at the end of the time horizon (60 years) is considerably higher than zero (e.g. average probability of being alive at the end of the time horizon is 26.7% in the metreleptin arm). This seems implausible to the

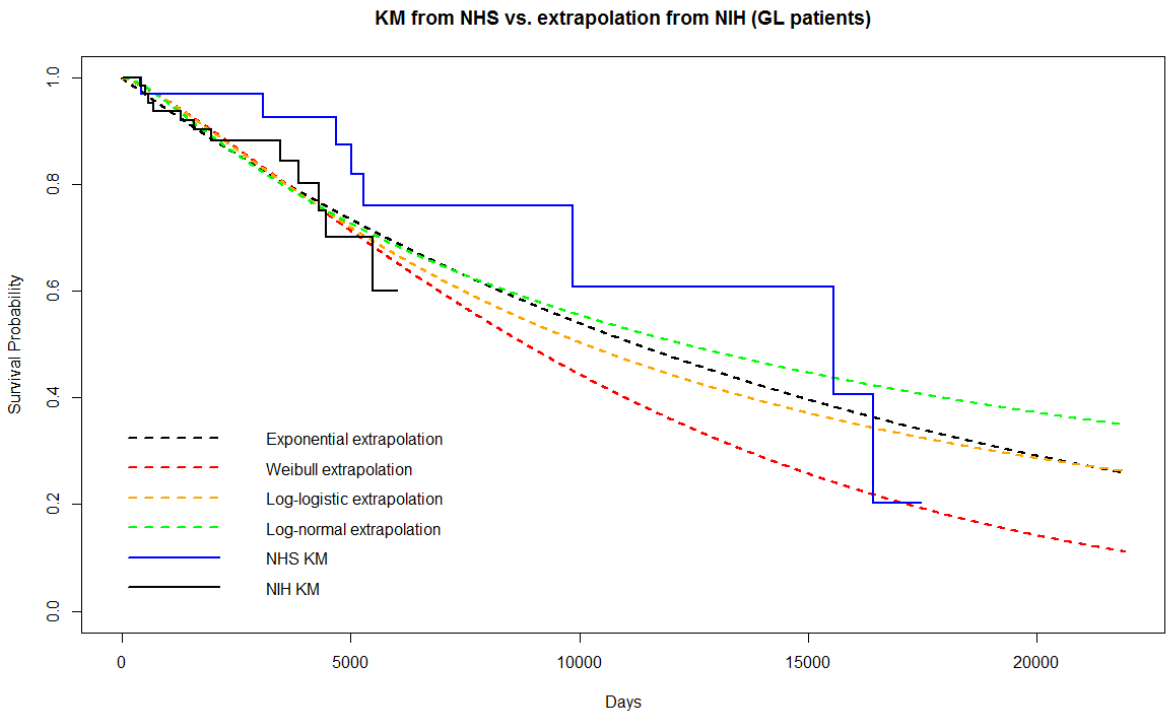
ERG, considering that the time horizon of the model was stated by the company to be lifetime. Therefore, the ERG asked the company to extend the time horizon, such that the average percentage of people alive at the end of the time horizon is almost zero. In its response to the clarification letter, the company provided an updated version of the model with a time horizon of 90 years.[39]

Not checking the clinical plausibility of the GL survival extrapolation

For the mortality of GL patients, data from the NIH follow-up was used, and in the extrapolation of that data, the approach as outlined by Latimer et al. 2013 was followed, but it appears that a crucial step mentioned in Latimer et al. was not included, i.e. checking the clinical plausibility of the extrapolated part of the curve.[88] Hence, the ERG asked the company to provide external data or expert opinion to assess whether another parametric function than the exponential should be used in the base case.

The company, in its response to the clarification letter, presented the results from a validation exercise using survival data from the GL/PL natural history study. The validation exercise compared the KM curve from the GL patients from the NIH follow-up study with that from the GL/PL natural history trial after an age-based adjustment procedure had been applied. The resulting KM curves can be seen in Figure 4 below.

Figure 4: Extrapolation validation for GL patients



Source: Figure 1 in the first response to the CL.[39]

The ERG had difficulty in interpreting the results of this validation exercise. Firstly, the age-adjustment procedure applied to the GL/PL natural history study patients was not clear.

Secondly, Figure 4 above suggests that patients receiving SoC live longer and the additional KM curve says nothing about the relevance of choosing an exponential distribution for the extrapolation. Therefore, the ERG disagrees with the company's interpretation of this graph, which states: "The graph in Figure 1 shows that the exponential extrapolation is in line with this constructed KM curve from the Natural History study".(Response to clarification letter, page 47) [39]

The assumption that survival is affected only by age, gender, type of lipodystrophy and number of organs impaired

The results from Table 75 (CS, page 266) suggest that the number of impaired organs is a significant covariate,[1] but the ERG questions whether this is the only significant covariate, noting that p-values alone might not be the only decision criteria for which covariates to include.

Therefore the ERG asked the company to provide all relevant details (dataset used, statistical codes compiled as well as all statistical outputs from the analyses including all relevant goodness of fit results) for the survival analysis exercises conducted (base case and sensitivity analyses in Table 75 from the CS), with their explanations, and to provide other prognostic survival models with additional covariates (for example type of LD, treatment received and any other relevant covariates), on the GL/PL natural history dataset, NIH follow-up study dataset and the pooled dataset, including only label-eligible patients.

The company, in its response, provided only the outputs of the sensitivity analyses conducted in Table 75 of the CS, on the full GL/PL natural history dataset. The company did not conduct any additional analyses.

The ERG considers that the concordance, R^2, and other goodness of fit statistic results provided by the company seem to compare the model in consideration with the null model. The model analysed in sensitivity analysis 4 (CS, Section 17.6.2.3, Appendix 6, pages 265-267) seemed to provide a better fit than a model based on number of organ impairments only.[1] However, the ERG could not check the statistical codes and the original data in detail and acknowledges that this analysis was not conducted on a pooled dataset, given the timelines. Therefore, the ERG is not certain if the function in sensitivity analysis 4 would be the most plausible predictive survival function that can be ever constructed from the data available from NIH follow-up study and GL/PL natural history study datasets.

Wrong derivation of the conditional survival curves given a fixed number of organ impairment

In the CS, the conditional survival curves given a number of organ impairment were derived from the final baseline GL and PL survival curves (Figure 38 and 39 in the CS, Section 17.6.2.2, Appendix 6, pages 260-261). In these derivations, it was assumed that these baseline survival curves correspond to the survival of patients that were having a fixed number (2.76) of organ impairments. This fixed number, 2.76, was stated as the average number of impaired organs in the NIH follow-up study and was used (together with the hazard ratios of an additional organ impairment for PL and GL patients as given in Table 27 above) while scaling the baseline

survival curves to conditional survival curves for PL and GL patients having zero, one, two and four organ impairments in the baseline.

The ERG considers that this approach is implausible, since the number of organs is not a fixed number throughout a patient's life, but rather a time variant parameter. The average number of impaired organs was 2.76 at the start of the NIH trial, but it was probably much higher (close to four), after 10/20 years. Therefore, the baseline survival curves do not represent a patient population whose number of organ impairments stayed fixed, hence scaling these curves based on this assumption, to conditional survival curves in Figures 5.2 and 5.3, probably overestimated the difference in survival at later time points in the conditional survival curves (i.e. it is expected that after many years, the number of impaired organs will be similar in all patients, independent from the number of organs impaired at the baseline).

5.3.3.3 Matching

The transition probabilities from the GL/PL natural history study (Table 70, CS, Section 17, Appendix, page 257) were not used in the economic model, because the company argued that the baseline characteristics of the GL/PL natural history and the NIH follow-up studies differ substantially (Table 76, CS, Section 17.6.2.4, Appendix 6, page 270), and the patients who were treated with metreleptin were, on average, at a more advanced stage of disease at the start of observation compared to the untreated (under SoC) patients.[1] Therefore, the company used *de novo* organ impairment progression transition probabilities for the SoC arm, derived from the same analysis, described in 5.3.3.1, conducted on a matched subset obtained from the GL/PL natural history study.

Matching methodology

The matching exercise created pairs of patients from both studies. For each treated patient from the NIH follow-up study, an untreated patient at a particular age from the GL/PL natural history study was found, whose reference age matched the treated patient's age at the start of treatment and whose level of organ abnormality at that age was close to that from the matched treated patient, was identified. *A priori* determined weights (α, β) were also assigned to the age and initial number of organ impairments, and gender ($1-\alpha-\beta$) of the patients; patients of the same gender were matched, as far as possible.

Treated GL patients were only matched to untreated GL patients and similarly, treated PL patients were only matched to untreated PL patients. For each treated patient in the NIH follow-up study, the algorithm searched through each pseudo patient generated from the GL/PL natural history dataset (each pseudo patient was generated by specifying a reference age). The pseudo-patient that minimised the weighted sum of the distances from the corresponding treated patient's baseline characteristics (*Diff*) was selected and that pseudo untreated patient was matched to the corresponding treated patient. The same untreated pseudo-patient can be matched with multiple treated patients in the NIH follow-up trial. The algorithm used in pairing the treated and untreated patients is reproduced in Box 1 below.

Box 1: The algorithm used in pairing the treated and untreated patients

Description of the matched cohort

1.) Subset GL/PL patients in the treated and untreated groups so that patients are only matched GL to GL and PL to PL.
2.) Create pseudo-patients with different starting ages.
    - For example, a patient who died or was censored at age 27 is split into 27 different "pseudo-patients," with a starting age of 0, 1, 2 … 24, 25, and 26.
3.) Find the difference (*Diff*) of each parameter (age, gender, initial number of organs impaired) between each treated patient and each untreated pseudo-patient. (For gender, males were coded to be 1 and females 0.)

Diff = (Absolute difference between the treated and untreated individuals) / (Standard deviation of the absolute difference between the treated and untreated individuals)

4.) Match each treated patient without replacement to the untreated pseudo-patient that minimizes an objective function (a weighted average of the differences in age, gender, and initial number of organs impaired).
    - The objective function took the form:

$\alpha * Diff(Age) + \beta * Diff(Initial\ Organ\ Impairment) + (1 - \alpha - \beta) * Diff(Gender)$

Being able to set the weights α, β allows for a flexible approach where changes to the relative importance of each characteristic for measuring the distance between treated and untreated patients can be made.
The weights were set as $\alpha = 0.35$ and $\beta = 0.35$ in the final version of the analysis.

Description of the matched cohort

The company's matching approach resulted in a list of pairs of treated patients and untreated pseudo-patients. The sample statistics of the treated and untreated patients are provided in Table 28, below.

Table 28: Sample statistics of treated and matched untreated pseudo-patients

	Treated patients (from the NIH Follow-up trial)	Untreated matched pseudo patients (generated from the GL/PL Natural History study)
Age at first symptoms (mean)	13.33	13.94
Age at start of treatment (mean)	24.28	25.51
Number of impaired organs at start of treatment (mean)	2.52	2.36
Number of mortality events (count)	13	31
% male	16.96	16.96
Source: Table 10 in the first response to the clarification letter, page 60[39]		

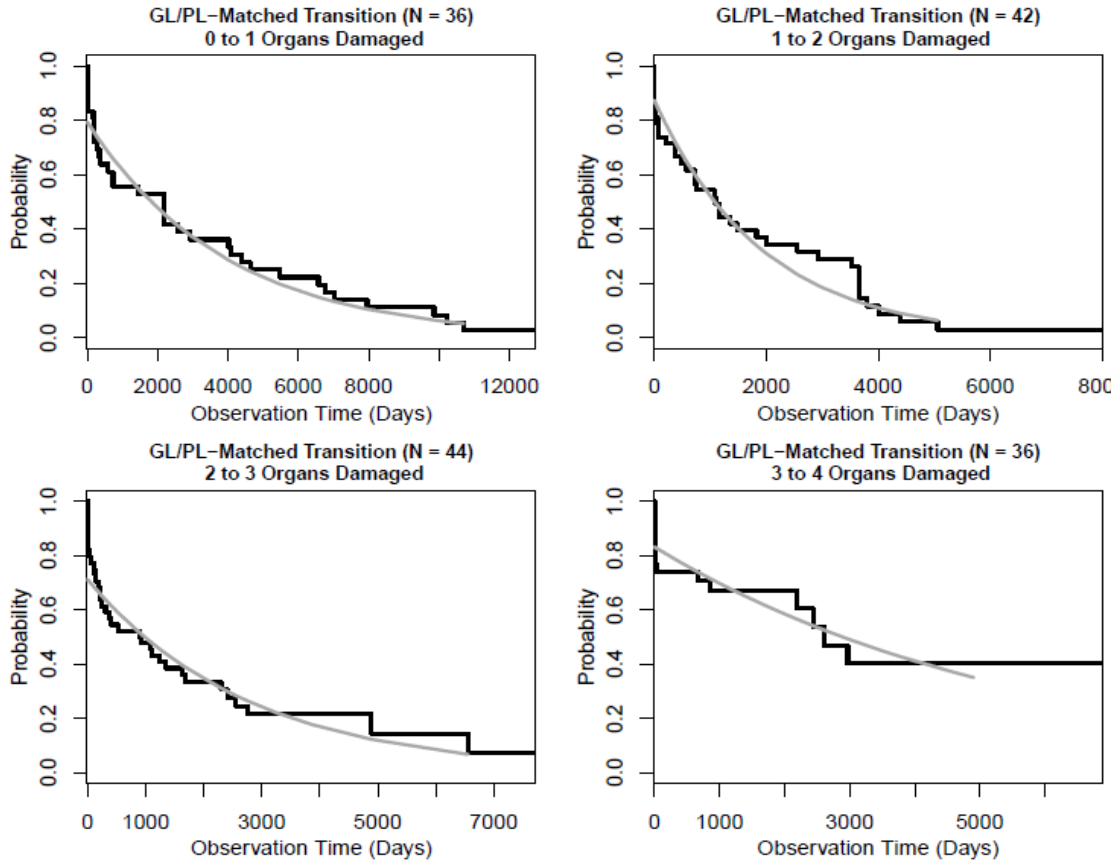
Extrapolation of organ impairment progression based on the matched untreated patient population

The same methods of analyses as described in Section 5.3.3.1 for SoC were applied by the company, but on the matched untreated pseudo-patients.

The KM and the fitted exponential curves for disease progression from the matched untreated pseudo-patients and the resulting progression probabilities obtained from the fitted exponential curves are given in Figure 5 and Table 29, respectively. In Table 29, the transition probability results obtained from the full GL/PL natural history study population are also presented, in order to show the impact of the matching exercise on the probability estimations.

The economic model uses the transition probabilities from the matched untreated pseudo-patients given in Table 29 as input. As can be seen from Table 29, the matched population's transition probabilities were higher in comparison to the results from the full GL/PL natural history study population, for transitions from 0 to 1 organ impairment, from 1 to 2 organ impairments, from 2 to 3 organ impairments. The transition from 3 to 4 organ impairments remained more or less unchanged.

Figure 5: Organ abnormality progression among matched natural history patients



Source: Figure 42 in the CS.[1]

Table 29: Estimated progression probabilities for the full GL/PL natural history study population (N=178) and for the matched untreated pseudo patients (N=47)

Full GL/PL Natural History study population			
Progression event	**Estimated progression probability**	**Number of patients at risk**	**Number of progressions**
0 to 1	6.7%	142	127
1 to 2	13.3%	151	112
2 to 3	11.0%	120	76
3 to 4	6.4%	77	30
Untreated matched pseudo patients (generated from the GL/PL Natural History study)			
Progression event	**Estimated progression probability**	**Number of patients at risk**	**Number of progressions**
0 to 1	8.9%	36	36
1 to 2	17.3%	42	39
2 to 3	12.3%	44	36
3 to 4	6.2%	36	16
Source: Tables 70 and 78 in the CS.[1]			

ERG comment:

The ERG has several concerns surrounding the matching exercise conducted by the company and how the results from these analyses were implemented in the electronic model. The main issues are listed below:

1. Appropriateness of the company's approach to the use of data to inform the estimates of treatment effectiveness
2. Lack of clarity regarding the matching algorithm used by the company
3. Independent estimation of the organ impairment transition probabilities from the treated and the matched untreated patient datasets
4. Lack of interpretation of the results

<u>Appropriateness of the company's approach to the use of data to inform the estimates of treatment effectiveness</u>

The ERG disagrees with the company on the appropriateness of the approach followed for analysing the evidence from the observational studies. In the NICE DSU TSD 17, some guidance has been provided for the selection of methods. In particular, a summary overview of the method selection algorithm as depicted in Figure 1, Figure 2 and Figure 3 in the TSD 17 document (p37-39).[90]

The company stated that the matching method employed in the CS was in line with NICE TSD 17, as it resembled the "nearest neighbour matching method", which was, according to the company, one of the two recommended matching methods (together with the propensity score matching) in NICE TSD 17. In the nearest neighbour matching method, a multivariate measure

of distance (typically the Mahalanobis distance) is minimised between the matched pairs. Since Mahalanobis distance was mentioned in the NICE TSD 17 as a typical example, the company, in its response to the clarification letter, provided results for an additional matching exercise, which minimises the distance between the treated and untreated cohorts based on the Mahalanobis distance.[39] In the latest submitted electronic model, the company used the transition probabilities derived from the matched untreated population based on the Mahalanobis distance minimisation method. The impact of this method and data updates on the transition probabilities used in the electronic model will be explained in Section 5.3.4.

The ERG considers that the NICE TSD 17 recommendations were misinterpreted by the company. Firstly, the nearest neighbour and propensity score matching methods (using distance measures such as Mahalanobis distance) were only mentioned as the most popular methods and they are not explicitly recommended *per se*.[39] In order to follow the actual recommendations in NICE TSD 17, the algorithm illustrated in Figure 2 and Figure 3 of that report should have been considered.[39]

The ERG notes that all of the steps depicted in Figure 2 from NICE TSD 17 were omitted. No discussion on the reasonability of the "no unobserved confounding" assumption was provided.

Furthermore, even after skipping all the necessary steps in Figure 2, the company employed some of the steps given in Figure 3 in an *ad-hoc* manner. The overlap between the treated and untreated groups before the matching and the balancing of the covariates after the matching were not assessed in a systematic way. No multivariate regression was conducted on the matched sample to estimate the treatment effect.

The selection of the covariates used in the matching (age, gender and number of organ impairments) was not based on a systematic selection procedure. Some of the influential observed confounders (e.g. the type of the organ impaired) were not included in the matching analysis. This might be problematic, since in the statistical analyses provided in the first response to the clarification letter document (Question B3.e.3, Response to clarification letter, pages 40-43), it can be seen that the type of the organ impairment had a significant impact on the transition probability estimates for the number of impaired organs.[39]

<u>Lack of clarity regarding the matching algorithm used by the company</u>
In the matching algorithm used by the company, for each patient died/censored in the GL/PL natural history study, pseudo patients that died/censored patient were created. It is not clear to the ERG how these pseudo patients were generated. The code provided by the company gave some errors and the ERG is especially concerned if the starting number of impaired organs for these pseudo patients remains the same as their starting ages increase. Omitting to update the starting number of impaired organs while updating the starting age of a pseudo patient would create a bias in favour of the metreleptin arm.

Furthermore, it was not obvious why a weight of 0.35 was chosen for the starting age and the initial number of impaired organs in the base-case. The ERG considers this choice to be

arbitrary, and the weights should reflect the relative impact of each of the covariates on the estimated treatment effect.

Independent estimation of the organ impairment transition probabilities from the treated and the matched untreated patient datasets

The organ impairment transition probabilities for the treated and the matched untreated patients were estimated from different datasets, independently. The ERG noted that the CS did not include any sort of justification of this approach, and questions why the treatment effect was not estimated from a pooled dataset.

Lack of interpretation of the results

The ERG considers that insufficient interpretation of the matching results was provided. The size of the untreated matched dataset (N=47) is approximately one third of the treated patients' dataset (N=112); this suggests that an untreated patient is matched to multiple treated patients from the NIH follow-up trial. The implications of this were not discussed sufficiently in the CS.

Furthermore, it is not clear if the treatment shows a benefit for patients with a low number of organ impairments. In the covariate adjusted analyses conducted on the pooled dataset (NIH follow-up and the matched untreated) provided in B3.e.3 (Question B3.e.3, Response to clarification letter, pages 40-43),[39] the treatment was not a significant covariate in most of the analyses.

Given the lack of discussion on the "no unobservable confounding" assumption, the arbitrary selection of covariates (omitting many other observable confounders such as the type of organ impaired), the arbitrary selection of the methods, and how the treatment effect is estimated from the matched datasets, the ERG considers that the clinical inputs (resulting from the matching and the corresponding survival and organ impairment transition probability estimation exercises) used in the cost-effectiveness part of the submission are not trustworthy.

5.3.3.4 Other attributes (blood-lab and attributes other than organ damage)

In the extrapolation of blood-lab attributes (i.e. HbA_{1c} and triglyceride values), for the metreleptin arm, real-world data from the NIH follow-up study are used directly, to populate the model until the last time data are available. When real-world data become unavailable, the last observation carried forward (LOCF) method is used to extrapolate blood-lab attributes and the last observed data is assumed for all the periods until the end of the time horizon. For the SoC arm, the baseline blood-lab attribute values from the NIH follow-up study are assumed to remain unchanged throughout the whole time horizon.

In the extrapolation of the remaining attributes other than blood-lab and organ damage (i.e. hyperphagia, ability to work, reproduction, physical progression and fast progression), for the metreleptin arm, in some of the patients, some of the disease attributes are assumed to improve from the baseline value. This improvement is assumed from the first cycle and onwards until the end of the time horizon. It is stated that these improvements were based on the observed

patterns in the NIH follow-up study. For the patients in the SoC arm, all these disease attributes are assumed to remain unchanged from their baseline values until the end of the time horizon.

ERG comment:
The ERG has several concerns surrounding the extrapolation of blood-lab and other attributes (other than organ damage), conducted by the company in the electronic model. The main issues are listed below:

1. Lack of clarity regarding the real-world data from the NIH follow-up trial used for the attributes
2. Lack of clarity about the attributes that were included in the model
3. The extrapolation method assumed for the blood lab attributes
4. The extrapolation method assumed for the other attributes

Lack of clarity regarding the real-world data from the NIH follow-up trial used for the attributes
In the economic model, for each patient, a maximum of two measurements were provided for the following attributes: hyperphagia, ability to work, reproduction, physical progression and fast progression. For each of these attributes, the values under the "0" column were used for the SoC arm patients and the values under the "1" column were used for metreleptin arm patients. It is stated, in the company submission, that the values under the "1" column indicate the improvement from the baseline, however, details on the size/definition of these improvements were not provided. Therefore, the ERG requested detailed information on these attributes.

The company provided the following details in its response to the clarification letter:

"Hyperphagia and Impaired ability to work/attend school were coded directly from clinician's notes indicating the presence or absence of these attributes before metreleptin treatment and the improvement of the condition after metreleptin treatment. Improvement in impaired physical appearance was determined by improvement in any of acanthosis nigricans, hyperkeratosis, or hirsutism by the last NIH visit date. Improvement in disruption to female reproductive function is determined by improvement in any of irregular menstruation or polycystic ovary syndrome (PCOS) by the last NIH visit date. For an underlying issue to be improved as of the last visit date, the patient must have had the issue at baseline, and cannot have experienced any new emergent issues in the follow-up period specifically for that issue. In the case that one underlying issue present at baseline did not improve, while another issue present at baseline did improve, the patient is considered to have improved."(Response to clarification letter, page 28)[39]

The company's explanation lacks any objective, measurable definition of a clinical improvement for these attributes. The ERG cannot judge the reliability of the improvement data on these attributes, based on the information supplied.
Furthermore, in the electronic model, where real-world data were missing, the missing value was automatically assumed to be "0". The ERG asked whether this was a programming error or a deliberate assumption. The company acknowledged that it was a deliberate assumption,

stating that they expect that any impairment would be likely to be indicated in the patient's medical data. Thus, when there is no evidence of an attribute being present, it was typically assumed that it was absent.

The company stated that the only exception would be hyperphagia, stating that this was unlikely to be documented unless physicians were prospectively asked to assess it, whether or not it was present.

The company corrected the electronic model in the new version submitted, together with its response to the clarification letter. In the corrected model, patients with no hyperphagia data in period 1 were considered to experience the average treatment effect of metreleptin for their relevant group (i.e. patients with hyperphagia at baseline who lack metreleptin treatment data at period 1, will be assumed to have a hyperphagia with a probability of 0.09 in period 1 and onwards, since 9% of patients in the real-world data who suffer from hyperphagia at baseline continued to have hyperphagia in period 1).

The ERG deemed these imputation approaches as speculative, since they were not based on evidence, but rather on assumptions/expectations.

Lack of clarity about the attributes that were included in the model

In the CS, neuropathy, amputation and retinopathy were named in the list of attributes used in the electronic model, which characterised an individual patient's health (CS, Section 12.1.6, page 158).[1] However, in the electronic model, the ERG was unable to find these attributes.

The company confirmed that these attributes were not included in the cost effectiveness model and admitted the reporting error in the CS. They explained that these attributes were included in the discrete choice experiment (and thus utility decrements estimated), however, since the data on these attributes were not systematically available in the NIH follow-up study, the company decided not to include them in the model.

The extrapolation method assumed for the blood lab attributes

It was not clear to the ERG why only a "last observed carried forward" approach was followed in the extrapolation of HbA_{1c} and triglyceride levels. Therefore, the ERG asked the company to justify their choice of extrapolation approach and explore other methods for HbA_{1c} (e.g. regression imputation or assuming a linear increase) and triglyceride (e.g. mean imputation) extrapolation.

In the updated version of the electronic model submitted with the company's response to the clarification letter, a scenario analysis is conducted where each patient under metreleptin was assumed to experience the same annual change in his/her blood-lab values that s/he experienced during the period when real world data were collected. On the other hand, for patients under SoC, a 0.01 percentage point increase of HbA_{1c} and a 1 mg/dL increase in triglyceride level were assumed each year. The ERG considers these scenario analyses uninformative, as the extrapolation parameters for the blood-lab values were arbitrarily chosen.

The company stated that the NIH follow-up study suggested some improvements in the blood-lab values, but there was variation between patients. They further stated that no specific trend was observed in the GL/PL natural history study. The company rationalised its extrapolation choice by claiming that the LOCF approach would be conservative, however, the ERG questions the validity of this claim, since substantiating such a claim requires a comparison of these longitudinal blood-lab values from both studies in a statistical analysis.

In general, the ERG does not agree with the assumptions of the company base-case and in the additional scenario analysis. Assuming that the blood-lab values would remain constant or keep on decreasing in the metreleptin arm cannot be considered as conservative, given the outstanding uncertainties about the anti-drug antibodies and long-term efficacy.

The extrapolation method assumed for the other attributes

The "Progression Speed" attribute has an impact on QoL and cost calculations but it has no influence on the disease progression probabilities in the model. The ERG had the impression that this attribute was related to the speed of disease progression, and hence the disease progression probabilities would be affected by this attribute. Therefore, the ERG requested additional details on the "fast progression" attribute and justification for the exclusion of this attribute's impact on the disease progression probabilities.

The company stated that the progression speed attribute was included to illustrate the disutility associated with living with an aggressive and progressive disease. Patients were categorised as experiencing fast progression at baseline if they developed more than one organ abnormality per nine years of age prior to metreleptin initiation. Patients were categorised as continuing to experience fast progression after metreleptin initiation if the next organ abnormality was observed within three years of metreleptin initiation.

The ERG considers this categorisation to be problematic, since the time frame used to define improvement was shorter than the time frame used to identify the existence of the attribute at base line (three years vs. nine years). Furthermore, the ERG remains unconvinced about the validity of excluding the impact of the "fast progression" attribute on the disease progression probabilities. The ERG expects that patients having this attribute would have different transition disease progression probabilities than patients without the attribute.

It is not clear to the ERG how the ability to work data and improvement in ability to work data were categorised in the NIH follow-up trial. Also, the ERG notes that the probabilities for being unemployed, partially employed and being retired were not incorporated in the calculations. The ERG is not certain if an improvement in the employment status of a patient would be directly attributable to the intervention.

Given the uncertainties and the lack of reliability of the collected data, the ERG requested alternative scenario analyses from the company, such as a scenario where the baseline and follow-up attribute values are the same in both metreleptin and SoC arms. In addition, another scenario analysis was requested, where these attributes do not stay constant but change over time. The company provided these scenarios embedded in the updated version of the electronic

model submitted together with the company's response to the clarification letter.[39`] The impact of the same non-organ/non blood-lab attribute levels was also examined in the ERG exploratory analyses in Section 6.

5.3.3.5 Adverse events

Only hypoglycaemia was incorporated in the economic model as an adverse event. In the metreleptin arm, the real-world data from the NIH follow-up study were used directly, to populate the model until data were no longer available. When real-world data became unavailable, mean imputation (for that specific patient until that specific time) was used to extrapolate the number of hypoglycaemia events per year until the end of the time horizon.

For the SoC arm, it was assumed that patients do not experience hypoglycaemia events. The justification of this extrapolation approach was not given in the CS.

ERG comment:

It was not clear to the ERG, if all hypoglycaemia events that the NIH follow-up patients experienced were collected systematically.

In addition, the ERG cannot understand why no adverse events, other than hypoglycaemia, were incorporated in the model (such as neutralising antibodies, fatigue, injection site issues, decreased weight, lymphoma, or impact of pancreatitis following discontinuation). It should be noted that the lymphoma risk was subject to a REMS in the FDA appraisal.[75]

The company stated that, beyond the prevalence of an adverse event, the following considerations affected the decision on the inclusion of an adverse event in the cost effectiveness analysis: i) whether these AEs were likely to be caused by metreleptin (vs. were a feature of lipodystrophy, since no control arm was available), ii) the availability of control data (e.g. baseline or pre-baseline information) and iii) whether the potential impact on cost effectiveness could be significant (e.g. vs. marginal).

The company stated that fatigue accounted for 7.3%-9.1% of total treatment-emergent AEs within lipodystrophy subgroups in the NIH 991265/20010769 study. However, their discussions with one of the clinical experts (Dr Brown at NIH), suggested that there was no significant increase in fatigue associated with the use of metreleptin.[39] They further stated that adequate information on fatigue prior to treatment with metreleptin was not available from chart data at NIH, thus a decision was made not to include of fatigue in the cost effectiveness assessment.

Based on the present neutralising antibody assay, the company noted that neutralising antibodies accounted for up to 6.1% of all AEs reported in GL patients, and 0% of all AEs reported in PL patients, and for the majority of these patients the impact on efficacy was transient. The company believes that further inclusion of neutralising antibody considerations, though potentially important clinically, would not have a large impact on the cost effectiveness assessment, since other markers for clinical efficacy were incorporated in the model already. The ERG disagrees with the company's argument, since the loss of efficacy was not captured

in the model. The real-world data from the NIH follow-up study was used in populating the model, but loss of efficacy was obviously not considered for the extrapolations of the blood-lab attributes and of the other attributes (e.g. hyperphagia, ability to work, etc.). Note that the anti-drug antibodies and the potential implications for long-term efficacy were the subject of the second REMS in the FDA appraisal.[75]

The company stated that all injection site issues in the NIH 991265/20010769 study were moderate, non-serious, and did not lead to treatment withdrawal. According to the company, the prevalence of such issues was low, occurring in between 6-7% of patients, depending on the lipodystrophy subgroup (GL vs PL) analysed. Consequently, their impact on cost effectiveness considerations was seen as likely to be marginal and they were not included in the analyses.

The company stated that weight decrease occurred commonly in the NIH 991265/20010769 study: accounting for 25.8% of total AEs reported in GL patients, and 4.9% of total AEs reported in PL patients. However, according to the company, excessive weight loss concerns were generally addressed by dose modification/reduction.

In the clinical effectiveness part of the CS, acute pancreatitis was listed as a treatment emergent adverse event and the company stated that abrupt interruption or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis. The treatment emergent acute pancreatitis risk due to metreleptin was not directly incorporated in the cost effectiveness analysis. When the ERG requested for a clarification, the company stated that the increased risk of pancreatitis due to metreleptin discontinuation was incorporated indirectly in the electronic model, by applying the organ impairment risks from the SoC arm for the patients who discontinue metreleptin. Even though the organ impairment risks from the SoC arm are higher than those from the metreleptin arm, the ERG considers that this increase in organ impairment risks is attributable to the situation of not receiving metreleptin treatment in the long-run and therefore does not actually represent the risk of acute pancreatitis as a treatment emergent adverse event, which might be due to abrupt interruption or non-compliance as well as other reasons.

The ERG partially agrees with some of the justifications provided by the company on the exclusion of some of the adverse events (e.g. injection site issues), but some of the assertions by the company were not evidence based and solely based on beliefs or expert opinions. Furthermore, the ERG has the impression that some critically important adverse events (e.g. neutralising antibodies and treatment emergent acute pancreatitis) were overlooked in the cost effectiveness analysis, which created a bias in favour of metreleptin. Compared to the many other issues in this economic evaluation however, the impact of this bias may be rather small.

5.3.3.6 Discontinuation

In the metreleptin arm, the patients are at risk of discontinuation from the metreleptin treatment.

The real-world discontinuation data from the NIH follow-up trial were used in the cost effectiveness analysis until data were available. After the point, where data were no longer

available, a weighted overall average value of 2.047% for the discontinuation rate is applied to the patients who are still on treatment at the last observation point, at each cycle until the end of the time horizon.

Discontinuation from metreleptin treatment has implications for drug acquisition costs and organ impairment progression transition probabilities (for discontinued patients, related parameters from the SoC arm are applied).

ERG comment:
In the calculation of the overall average discontinuation value of 2.047%, the discontinuations in the first period were excluded. The company justified this exclusion by the fact that the observed discontinuation data were available for period 1 for all patients and because the pattern of discontinuation in the short term (<1 year) may be substantially different than the discontinuation in the long run. The ERG considers that this exclusion might lead to bias if no statistically testing is conducted on the difference between short term and long-term discontinuation trends.

In addition, besides the drug acquisition costs, the model only reflects the impact of discontinuation in the organ impairment progression (i.e. when a patient discontinues, metreleptin, organ progression transition probabilities for SoC will be used for that patient). The ERG considers that the impact of discontinuation should also be reflected in other disease attributes, (e.g. blood-lab values, hyperphagia, ability to work etc.). Not including the impact of discontinuation on these attributes created a bias in favour of metreleptin. In Section 6, in the exploratory analyses, the impact of discontinuation on other attributes than organ impairment will be investigated.

5.3.3.7 Health-related quality of life

The company conducted a discrete choice experiment (DCE) on a large sample of the general population with the aim to provide reliable estimates of HRQoL "disutilities" associated with key lipodystrophy attributes. In this section, first the DCE study conducted by the company is summarised and critiqued. After the summary of the DCE study, the incorporation of the DCE disutility estimates to the economic model is explained.

Discrete choice experiment study

Details about the study methods and results were provided in Section 17, Appendix 5 of the CS.[1] The main features of the DCE study are summarised below.

Study design

The study analysed data generated by a DCE in which respondents had to choose between two hypothetical health profiles that differed in levels of organ impairment, disease attributes and life expectancy.

Sample selection

A market research firm, Survey Sampling International (SSI), surveyed 1,000 respondents from six countries: the US (250), UK (150), France (150), Germany (150), Italy (150) and Spain

(150). In the US, quotas were set in such a way that the final sample matched the US census on gender, age, region (Northeast, Midwest, South, West), and education. In each of the five European countries, quotas were set for the final sample to match Eurostat demographic characteristics for each country.

Survey

The survey consisted of three main components: (1) a demographic questionnaire, (2) a tutorial informing respondents of the disease and its associated attributes and (3) a conjoint survey in which participants had to choose their most preferred health profile from two choice cards. Choice cards were used to represent hypothetical patients and were constructed by assigning values to disease attributes and varying these values across the two cards.

The tutorial consisted of two parts whose topics are summarized in Table 30 below. The tutorials are fully presented in Appendix 17 – Section 5.4 of the CS.[1] After watching the tutorials, the participants answered a diagnostic question following each part. Those participants who spent less than four minutes reviewing the first part, or less than two minutes reviewing the second part were excluded from proceeding onto the conjoint survey and were not counted towards the respondent quota. Respondents were also excluded from the survey (and not counted towards the respondent quota) when incorrect responses to both diagnostic questions were given.

Table 30: Topics in each part of the survey tutorial

Part 1	Part 2
* Instructions for undertaking the survey * Description of survey pages * Example comparison screen (different for male or female respondents) * List of patient situation attributes * Lipodystrophy – An introduction * Organ damage * Heart damage * Liver damage * Kidney damage * Pancreas damage * Uncontrolled constant hunger (hyperphagia)	* Impaired ability to perform work/school work * Impaired physical appearance (different for male or female respondents) * Disruption to female reproductive functioning (female respondents only) * Depression * Chronic pain * Eye damage (retinopathy) * Nerve damage (neuropathy) * Amputation (e.g., toes, limb) * Impaired triglyceride (blood fat) control * Impaired blood sugar control * Risk of developing neutralizing antibodies
Source: Table D66 in the CS[1]	

The conjoint survey consisted of 14 choice tasks. For each task, participants had to choose between two choice cards consisting of 12 (out of a possible 20) attributes as indicated in Table 31 below. Attributes were shown in random order across respondents but in the same order for each respondent across tasks. Age and life expectancy were always at the top of the choice card and the position of organ abnormality attributes were randomised as a cluster.

Table 31: Summary of attributes and levels for discrete choice experiment

Features	Levels
Age	5 / 25 / 45
Life expectancy (expected age at death)	If age is 5: 15, 25, 45, 65 If age is 25: 35, 45, 65, 85 If age is 45: 55, 65, 85, 105
Remaining life years	= Life expectancy – age
Heart damage	Present / Absent
Liver damage	Present / Absent
Kidney damage	Present / Absent
Pancreas damage	Present / Absent
Progression of organ damage	No change / Slow / Fast
Ability to perform work / school work	Able / Unable
Uncontrollable constant hunger (hyperphagia)	Present / Absent
Impaired physical appearance	Present / Absent
Disruption to female reproductive functioning (Shown to women only)	No damage / Polycystic ovary syndrome / Infertility
Depression	Present / Absent
Chronic pain	Present / Absent
Eye damage (retinopathy)	Present / Absent
Nerve damage (neuropathy)	Present / Absent
Amputation (e.g., toes, limb)	Present / Absent
Triglycerides (blood fat) control	No response or worsening / Partial response / Achieved goal
Impaired blood sugar control	No response or worsening / Partial response / Achieved goal / Achieved goal with hypoglycemia
Risk of loss of response to treatment / Development of neutralizing antibodies	Standard risk / Increased risk due to development of neutralizing antibodies
Lymphoma (a type of blood cancer)	Standard risk / Increased risk
Source: Table D67 in the CS[1]	

QALY estimation

The data obtained from the conjoint survey was used to estimate a multinomial logit model, under the assumption that individuals derive utility from spending time in particular health states as in Bansback et al, 2012 and Viney et al, 2014.[83, 84] In particular, the utility function to be maximised based on the respondents' choices was the following:

$$U = T \times \left(\beta_0 + \sum_i \beta_i x_i \right) + \varepsilon$$

where T denotes the remaining life, β_0 denotes the coefficient quantifying how much utility was associated to one year of perfect health, β_i denotes the coefficient that quantifies the disutility generated by attribute i, x_i denotes an indicator variable which values "1" when attribute i is impaired, and ε denotes the error term.

For the two fertility attributes considered in the DCE, an additional indicator variable (taking a value "1" for females) was also included that multiplied the product of coefficient and attribute indicator variable.

Under a multinomial logit model, it is assumed that, when the utility of choice card A was greater than the utility of choice card B, it is more likely that A is chosen by the respondent. Choice cards also contained information about the current age of the hypothetical patient. This variable allowed stratification of QALY weights by patient's age, which potentially implied different weights for paediatric patients. However, in the utility function described above, age was not included, thereby introducing the potential for omitted variable bias. When age was included in the utility function, some coefficients (i.e. QALY weights) were significantly different (statistically) between patients of different ages. According to the company, excluding age from the utility function "implied that the analysis effectively calculated the QALY weights for a hypothetical patient of average age".[1]

Another assumption was to exclude the intercept coefficient from the utility function. This was done by the company for the sake of consistency, i.e. without intercept, the utility could be interpreted as that obtained from spending T years in a health state characterised by an attribute profile. Moreover, the utility of death was then equal to zero (since a health profile in which a patient dies implies that $T = 0$). This approach was also followed in Viney, et al 2014,[84] where the impact on the calculated QALY weights of including an intercept on the utility function was deemed negligible. The company indicated that the same happened in their case. The main difference was observed in the coefficients for the progression of organ abnormality, which changed by 20% across the two estimation approaches. However, the contribution of this single coefficient to the overall study conclusions was deemed negligible by the company.

After estimating the coefficients of the utility function as described above, QALY weights associated with each disease attribute were generated. These weights can be interpreted as the decrease in utility associated with attribute impairment as a fraction of the utility from spending one year in perfect health or simply:

$$QALY\ weight\ of\ attribute\ i = \frac{\beta_i}{\beta_0}$$

DCE Results

QALY weights obtained following the approach described above ranged from −0.27 for amputation to +0.03 for slow progression of organ damage. When the analysis considered only respondents from the UK, they ranged from −0.27 for amputation to -0.01 for slow progression of organ damage. All QALY weights obtained from all respondents and from UK respondents only can be seen in Table 32 below. Point estimates and confidence intervals shown in Table 32 were calculated by bootstrapping the QALY weights obtained from the multinomial model. Most of the point estimates based on UK respondents were different from those based on all respondents, and all confidence intervals are much wider, as a result of the smaller sample size.

Table 32: Per-period disutility toll from lipodystrophy-related complications

	All samples		UK only	
Health State	**Utility Value**	**95% Confidence Interval**	**Utility Value**	**95% Confidence Interval**
Heart abnormality	[redacted]	[redacted]	[redacted]	[redacted]
Liver abnormality	[redacted]	[redacted]	[redacted]	[redacted]
Kidney abnormality	[redacted]	[redacted]	[redacted]	[redacted]
Pancreas abnormality	[redacted]	[redacted]	[redacted]	[redacted]
Slow progression of organ abnormality	[redacted]	[redacted]	[redacted]	[redacted]
Fast progression of organ abnormality	[redacted]	[redacted]	[redacted]	[redacted]
Unable to perform work/school work	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled constant hunger (hyperphagia)	[redacted]	[redacted]	[redacted]	[redacted]
Impaired physical appearance	[redacted]	[redacted]	[redacted]	[redacted]
Disruption to female reproductive functioning - Polycystic Ovary Syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Disruption to female reproductive functioning - Infertility	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]
Chronic Pain	[redacted]	[redacted]	[redacted]	[redacted]
Eye damage (Retinopathy)	[redacted]	[redacted]	[redacted]	[redacted]
Nerve damage (Neuropathy)	[redacted]	[redacted]	[redacted]	[redacted]
Amputation (e.g. toes, limb)	[redacted]	[redacted]	[redacted]	[redacted]
Triglyceride (blood fat) control – No response or worsening	[redacted]	[redacted]	[redacted]	[redacted]
Triglyceride (blood fat) control – Partial response	[redacted]	[redacted]	[redacted]	[redacted]
Impaired blood sugar control – No response or worsening	[redacted]	[redacted]	[redacted]	[redacted]
Impaired blood sugar control – Partial response	[redacted]	[redacted]	[redacted]	[redacted]
Impaired blood sugar control – Achieved goal with hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]
Increased risk of loss of response to treatment/development of	[redacted]	[redacted]	[redacted]	[redacted]

	All samples		UK only	
Health State	**Utility Value**	**95% Confidence Interval**	**Utility Value**	**95% Confidence Interval**
neutralizing antibodies (e.g. with additional medication)				
Increased risk of lymphoma (a type of blood cancer)	[redacted]	[redacted]	[redacted]	[redacted]
Source: Table 68 and 69 in CL[1]				

Validation

Three UK lipodystrophy clinical experts (Dr Rebecca Brown, Dr David Savage, and Dr Anna Stears, from the Addenbrooke primary treatment centre in UK) provided input for the survey and commented on the results. Input from the experts helped identify and prioritise the disease attributes included in the survey. The experts also provided input on the tutorial materials used in the second module of the survey.

Some utility decrement estimates from the DCE were compared to estimates from Ara 2011.[91] According to the company, this comparison "generally validated the settings of the new study" although some differences were observed as shown in Figure 6.[1]

Figure 6: Validation of utility decrement estimates vs published literature

Source: Figure 33 in the CS[1]

ERG comment:
Overall, the ERG has serious concerns about the validity and reliability of the QALY weights reported by the company. The key issue is that the use of DCE to directly obtain disutility values for heath states is still in its infancy. Whilst in the past years several important methodological issues have been resolved, several still remain. The most striking issue relates to the fact that DCE classifies health states far more often below zero than TTO and produces lower average health state values. Given the important consequences for cost effectiveness analyses, and the broad acceptance of health state values derived using TTO, the question inevitably arises: what is the explanation for this difference? Suggestions from literature concern issues related to anchoring (either at death = 0 or worst possible health state = 0), framing issues, or even that choices between cards may be driven not only by differences in utilities but also by how easy it is to compare alternatives.[92]

As long as these differences are not fully understood, the use of DCE disutilities to estimate QALYs remains highly speculative.

Besides this key methodological issue other major issues can be observed both regarding the design of the experiment and the analysis of the resulting data.

Choice cards
The attributes that were used in the DCE were selected based on interviews with clinical experts in the UK and the USA. However, it is common practice to include various stakeholders in the selection of relevant attributes, which in this case would have been for example the patients besides the already included clinicians.

Despite a direct question of the ERG in the clarification letter (Question B13.c) the company did not provide details regarding the potential for overlap and/or correlation between attributes. For example, uncontrolled lab values for blood glucose will lead over time to retinopathy and if respondents are aware of this, it may create correlation between the two attributes.

The three levels of age that were used in the choice cards pose a problem, as it groups children's age and adult ages together. In general, different instruments should be used for these two groups, as respondents tend to choose differently in children.

Another issue with the use of age as an attribute in the choice cards relates to the fact that the two options could state different ages. The choice question ought to be answered conditional on a certain age of the patient; it is impossible to judge what impact the use of two different ages in the choice cards may have had on the choices made.

Life expectancy as presented in the choice card (age + remaining years to live) is possibly subjected to misinterpretation, as it is not clear if respondents were fully aware that the life expectancy indicated time of death.

The colour coding used in the choice cards as illustrated in Appendix 17.5 of the CS[1] appears to be problematic. On each card, red is used for the least favourable level of an attribute *on that card* and green for the most favourable. Thus, colours are not fixed for specific attribute levels, but may be green in one comparison and red in the next. Even if the text would be removed from the coding cards, one could still get a preferred option just based on the colour coding.

Respondent selection from six countries

Combining preference results from six different countries raises the question to what extend this is methodological sound. The fact that for EQ-5D country-specific tariffs have been developed suggests that this may not be the case. Considering this, it is unclear to the ERG why the company has not opted to use the disutilities based on UK respondents only.

It is unclear whether a scaling parameter was included to account for pooling the data from six different countries.

It is also not evident whether the meaning of the attributes and levels is guaranteed in all countries after translation, by for instance doing a forward translation and back translation. With the current information, the ERG cannot properly assess whether this represents an issue or not.

Experimental design

The survey is very long and complex, with 12 attributes being shown per card. This raises questions regarding the respondent cognitive burden of the task. From the information provided by the company it is not clear if a check for respondent burden was included, through a pre-test for example, or post-hoc by checking consistency between the first six choice sets and the last six.

In the survey, choice cards presented to women included an extra attribute for disruption to female reproductive functioning compared to the choice cards for men. It is then unclear how this influences the results of the pooled analysis of male and female respondents. The systematic omission of certain DCE designs for men potentially leads to bias, as there is a risk that men may have never seen certain attribute levels if they only occurred in combination with the 'women's fertility attribute'. It appears to the ERG that it might have been better to use

different disutility weights for male and female patients, given the current design of the choice cards.

In the company submission, no information was provided regarding the experimental design of the DCE. Thus, the ERG asked for additional information in the clarification letter (Question B13.b). In their response, the company explained that a Partial Profile Design was used, to allow for the option of not showing all attributes on each choice card, but rather a subset of 12 attributes. However, no further information was provided. So, it is not evident if a (Bayesian) D-efficient design was used? Neither is it clear whether priors were used and if so, why and which. The ERG would also have preferred to receive details on the correlation matrix as the question may be raised to which extent the DCE-values are based on preference values or are (partially) a product of correlation in the design itself.

Using a sound experimental design for a DCE is of key importance to find valid preference values and the lack of details provided by the company make it very difficult to assess the design used by the company.

MNL model

The company explained in the CS that a multinomial logit model was used to analyse the choice data. As the choices were always between two alternatives, this reduces to a logit model. These models have three strong assumptions: independence from irrelevant alternatives (or IIA) assumption, the identical and independent distribution (IID) assumption for the error terms and preference homogeneity. No information was provided in the CS or in the response to the clarification letter regarding any formal testing to check if these assumptions are satisfied. A mixed logit model which allows for preference heterogeneity should at the very least have been tested. It is quite possible that this alternative model would have had a substantial impact on the results. Thus, the model used by the company is most likely too simplistic for decision making.

The company decided to use a model that did not include age of the hypothetical patient as attribute. Most likely, age had an impact on the weights of other attributes (through at least a two-way interaction) and thus the ERG does not agree with the interpretation given by the company: "Excluding age implied that the analysis effectively calculated the QALY weights for a hypothetical patient of average age."[1]

The company used a simple additive model to estimate the QALY weights. In this model, the intercept was excluded, and the company referred to Viney et al. 2014 as justification.[1, 84] However, whilst Viney et al. indeed report that the impact of including an intercept on the calculated QALY weights was negligible in their study, this does not provide any justification for omitting the intercept in general. Instead, the validity of such choice should have been tested separately in the current study.

Attribute and level selection

The selection of attributes and levels has not been determined with the target population. A pilot testing or at least asking patients which key symptoms are deemed important would have

been of great value. Clinicians' preferences are often not the same as patients or general population preferences.

Validity of QALY estimates

In the result section (Table D46), the company showed both the life-years accumulated in both treatment groups as well as the QALYs, without discounting. It is striking to see in that in the metreleptin group 35.7 life years were accumulated, translating into 15.3 QALYs, whereas for the SoC group 24.7 life years were accumulated, translating into a mere 0.65 QALYs. A simple division shows that this implies for the metreleptin group that patients experience on average a QoL utility of 0.43, whereas for SoC patients this value is 0.03. The latter implies that the average patient with lipodystrophy not receiving metreleptin values his/her health state as very close to death, which seems highly unlikely.

In conclusion, given all the major flaws in the design of the DCE and the analysis of the data, the ERG considers the disutility weights presented by the company as speculative. This assessment is further confirmed by the highly unlikely model results regarding life years and QALYs.

Application of the disease attribute disutility estimates in the economic model

In the model, health states for each individual patient are characterised by the combination of a set of attributes, which serve as indicators of impairment. These attributes include organ abnormality (liver, heart, kidney and pancreas), hyperphagia, female reproductive dysfunction/infertility, loss of ability to perform at work/school, impaired physical appearance and metabolic abnormalities (such as failing to control triglycerides and HbA_{1c} levels). Each attribute level is associated with a utility decrement obtained from the discrete choice experiment study described above. These attribute levels are valued at every model cycle (1 year) to define an overall health state utility per patient. Table 33 shows the utility decrements used by the company in the economic model. Deterministic sensitivity analyses considered a 50% deviation from the mean value for the lower and upper limits. In the PSA, every utility decrement was assumed to follow a Beta distribution with the mean and standard error shown in Table 33.

Table 33: Utility decrements used in the cost effectiveness analyses

Attribute	Mean value	Standard error	Source
Heart Abnormality	-0.19	0.047	Company DCE and assumptions[1]
Liver Abnormality	-0.15	0.038	
Pancreas Abnormality	-0.13	0.032	
Kidney Abnormality	-0.13	0.028	
Hyperphagia	-0.11	0.015	
Disruption to female reproductive function	-0.06	0.064	
Loss of ability to perform work / school	-0.25	0.047	
Impaired Physical Appearance	-0.10	0.025	
Triglycerides: Achieved Goal (<=200 mg/dL)	0.00	NA	
Triglycerides: Partial Response (>200 mg/dL, <=500 mg/dL)	-0.05	0.012	
Triglycerides: No Response (>500 mg/dL)	-0.11	0.028	
HbA_{1c}: Hypoglycemia	-0.01	0.004	
HbA_{1c}: Achieved Goal (>4.0, <=7.0)	0.00	NA	
HbA_{1c}: Partial Response (>7.0%, <=8.0%)	-0.08	0.02	
HbA1C: No Response > 8.0%	-0.18	0.045	
Source: Table D37 and the electronic model in the CS[1]			

ERG comment:

The utility decrements derived from the company's DCE were used in the economic analyses since the characteristics valued by the DCE were similar (but not identical) to those collected in the NIH study. The effect of changes in utility decrement values was explored via sensitivity analyses. However, there are several attributes that the company mentioned as having impact on the patient's quality of life, which were not included in the economic analyses without further justification. These include pain, depression, retinopathy, neuropathy and amputation.

Despite the significant number of adverse events described in Section 5.3.3.5, only hypoglycaemia was included in the cost effectiveness analysis as an adverse event (with an associated utility decrement). No effort has been made to quantify the possible impact of other adverse events on patients' quality of life.

The CS (CS, Section 12.1.3, page 151) states that the true utility decrement associated with hyperphagia is likely to be underestimated since, according to the company, the "DCE cannot fully encompass the patient experience of such a unique aspect of the disease".[1] To quantify the impact of the utility decrement associated with hyperphagia on the cost effectiveness analyses, the company presented a scenario where this decrement was doubled. For further discussion on the utility decrement associated with hyperphagia the company refers to Section

Error! Reference source not found., Appendix 5 in the CS.[1] The ERG considers that a similar iscussion and (when deemed necessary) scenario analyses on the remaining utility decrements should have been provided by the company.

The ERG identified some inconsistencies and programming errors in the cost effectiveness model submitted by the company. Firstly, the cell formula used in assigning disutilities to organ impairments in the metreleptin arm patients was different from that in the SoC arm, each formula followed different approaches with differing underlying assumptions. Secondly, both of the formulae used were not clear and not explained in the company submission. Finally, the ERG identified errors and logical inconsistencies in both of them.

The formula used in the metreleptin arm seemed to calculate the organ impairment associated disutilities from the real-world data (on the specific organ type impairment) until the data became no longer available. After that, the estimated cumulative number of organ impairments in each cycle was translated to the conditional probabilities for having a specific type of organ impairment at that cycle (e.g. probability of having a kidney impairment at a cycle given that the estimated total number of organ impairments is three at that cycle). In this translation, for each patient, the organ type assignment weights provided in Table D37 in the CS (CS, Section 12.2.6, page 164) were applied to the estimated cumulative number of organ impairments at each cycle independently, e.g. the probability that a patient has a kidney abnormality at a given cycle does not depend on whether or not that patient had a kidney probability in the previous cycle.[1] Furthermore, the ERG identified some errors in calculating the conditional probabilities (i.e. conditional probability of having specific type of organ impairment given a cumulative number of organ impairment). These errors led to inconsistent results, for instance, if the number of organ impairments of a patient at a given cycle is 4, the conditional probability for having a pancreas impairment would be equal to 1 (as well as having a heart, a liver or a kidney impairment). However, the formula used in the metreleptin arm, due to the errors in conditional probability calculations, provides incorrect estimates, for instance for some organs a probability value that is less than 1 and for the others a probability value that is more than 1.

In the formula used in the SoC arm, it was assumed that the type(s) of the organ(s) impaired at baseline stays impaired until the end of the time horizon. Therefore, the knowledge on the specific type of organ impairment at baseline was taken into account, while estimating the conditional probability for a specific organ impairment, given a cumulative number of impaired organs at a cycle. This seemed to be a more plausible approach, since some of the organ impairments are permanent conditions. However, the cell formula in the electronic model was not clear and not transparent and the ERG suspected some programming errors in this formula, such as using weights related to pancreas while calculating heart impairment related disutilities etc.

The ERG considers that the formula used in both arms to assign disutilities should be consistent. Therefore, in the corrected version of the company submission model, the ERG implemented the corrected version of the formula applied in the SoC arm to both arms. The impact of the correction of this error (together with the other programming errors) on the cost effectiveness results can be seen in the corrected CS base-case analyses in Section 6. In one of

the additional scenario analysis in Section 6, the ERG explored the impact of applying the alternative corrected formula from the metreleptin arm in both arms. Note that the same formulae were used while assigning organ impairment associated costs in the model, as well.

The systematic literature review conducted by the company identified only one study reporting on HRQoL in LD patients.[31] This study from Dhankar et al. 2015 collected data from the Lipodystrophy Connect Registry and reported an average estimated EQ-5D score associated with LD of 0.67. The ERG agrees with the company that EQ-5D domains might not provide an adequate perspective on quality of life for LD patients, and therefore the value reported by Dhankar et al. might not be fully appropriate.[31] However, given the lack of additional HRQoL data, and given the issues with the utility scores obtained by the DCE study as discussed previously, we present the results of some exploratory scenario analyses in Section 6, where the utility estimate from Dhankar et al. is multiplied by the life years gained obtained from the model, in order to get another estimate of QALYs gained (metreleptin vs. SoC).

5.3.3.8 Resources use and costs included in the model

Resource use associated with metreleptin treatment estimated using resource use questionnaires completed by two clinical advisers who treat lipodystrophy at Addenbrooke's Hospital.

Currently, only 11.3 mg vials (10 mg dose) metreleptin are available at a list price of £2,335 per vial. The availability of smaller vial sizes is expected within three months of submission of the variation to marketing authorisation, at a list price of £1,167.50 for a 5.8 mg vial (5 mg dose) and £583.80 for a 3 mg vial (2.5 mg dose). Based on the distribution (11.54% 10 mg dose; 69.23% 5 mg dose; 19.23% 2.5 mg dose) of observed current doses in the UK early access programme (EAP), an average annual per patient price of £434,633 is assumed in the analysis. Due to a loss of drug exclusivity after 10 years, a decrease of 90% of the list price of metreleptin was assumed in the model in one of the scenario analyses.

The costs related to standard of care treatment was estimated at £3,000 per patient per year.

In the CS, it was stated that the costs of home delivery and self-administration training will be funded by the company at no additional cost to patients or the NHS. Additional resource use costs, such as laboratory tests and office visits, are assumed to occur equally for both metreleptin and standard of care treatment and are assumed to be reflected in the nominal 'standard of care' costs. Standard of care costs were thus assigned to all patients in the model at each cycle.

A patient's health state is characterised by the presence or absence of abnormalities of the heart, kidney, liver, and/or pancreas. For each lipodystrophy-related complication, a patient's periodical costs are estimated based on their probability of occurrence of the complication and probability of survival in that period (Table 34). Unit medical costs for each complication were estimated based on NHS reference costs (Table 35). In the CS, it was stated that the following formula was used to estimate the cost per patient with organ abnormality:

estimated cost per patient with abnormality =

*(number of lipodystrophy-related inpatient stays per annum per patient / fraction of patients with abnormality) * cost per inpatient stay.*

In the model, no costs for hyperphagia, PCOS, inability to perform school or work, impaired physical appearance, or abnormal laboratory levels were included. Only adverse event cost of hypoglycaemia was included in the model at a price of £1,087.07 per hypoglycaemia-hospital admission.

Table 34: Estimated cost per patient with abnormality

Disease attribute	Estimated cost per patient with abnormality
Per-period medical costs from lipodystrophy-related complications	
Heart abnormality	£1,093.94
Renal abnormality	£590.04
Liver abnormality	£527.97
Pancreas abnormality	£44.28
Hyperphagia	£0
PCOS (Females Only)	£0
Unable to Perform School or Work	£0
Impaired Physical Appearance	£0
Per-period medical costs from non-achievement of triglyceride and/or glucose HbA_{1c} response	
Triglycerides Control	
Triglycerides: Achieved Goal (<=200 mg/dL)	£0
Triglycerides: Partial Response (>200 mg/dL, <=500 mg/dL)	£0
Triglycerides: No Response (>500 mg/dL)	£0
Glucose Control	
HbA_{1c}: Achieved Goal (<=7.0)	£0
HbA_{1c}: Partial Response (>7.0%, <=8.0%)	£0
HbA_{1c}: No Response > 8.0%	£0
Source: Table D40 in the CS[1]	

Table 35: National schedule of reference costs associated with lipodystrophy-related complication

Lipodystrophy-related complications	HRG currency codes
Heart abnormality	Weighted cost of total HRGs currency codes relating to coronary artery bypass: ED22A, ED22B, ED22C, ED23A, ED23B, ED23C, ED24A, ED24B, ED24C, ED25A, ED25B, ED25C, ED26A, ED26B, ED26C, ED27A, ED27B, ED27C, ED28A, ED28B, ED28C - NHS Ref costs relating to coronary artery bypass
Renal abnormality	Total of pre-transplant costs, transplant costs, and follow up outpatient costs. Total of LA10Z £232.52, + weighted cost of pre-transplantation workup costs LA11Z LA12A LA12B £373.44, + weighted costs of examination post-transplantation £233.69, + weighted cost of kidney transplant = £15716.14, + outpatient attendances for service code 102 £307.09
Liver abnormality	Weighted cost of total HRGs currency code GA01A, GA01B, GA01C, + outpatient attendances for service code 102 £307.09
Pancreas abnormality	Weighted average cost per FCE of elective inpatients, non-elective long stays, non-elective short stays for endocrine disorders KA08A, KA08B, KA08C
Source: Table D39 in the CS[1]	

ERG comment:

Currently, only 11.3 mg vials of metreleptin are available. In the submission, the availability of different vial sizes (5.9 mg and 3 mg) was assumed. The company confirmed, in their response to the clarification letter, that only 11.3 mg vials will be available at the time of marketing authorisation, but the approval of the other smaller vial sizes is expected within three months of submission of the variation.[39] All three vial sizes were used in the calculation of a weighted average annual drug acquisition costs for metreleptin (£434,633). This weighted average was based on the number of patients in Addenbrooke's Hospital expected to be treated with each vial size. The company adjusted the current dose mix at Addenbrooke's Hospital for potential increase. Therefore, they considered that six patients on 2.5 mg would be switched on 5 mg over time. The adjusted proportion of patients receiving each vial size is reported in Table 36. The detailed information on the adjusted vial use was not provided by the company (e.g. patient characteristics of the EAP patients were missing). Since the considered vial sizes are still not available yet, and the generalisability of the patients from the Addenbrooke's Hospital to the UK LD population, the ERG considers that there is a substantial amount of uncertainty on the drug acquisition costs for metreleptin.

Table 36: Proportion of EAP patients receiving each vial size

Vial	Proportion	EAP data
11.3 mg vial (administers up to a 10 mg dose)	11.54%	based on n=3
5.8 mg vial (administers up to a 5 mg dose)	69.23%	based on n=18
3 mg vial (administers up to a 2.5 mg dose)	19.23%	based on n=5
Source: Table 22 in the first response to the CL[39]		

The costs associated with standard of care are estimated at £3,000 and were applied to patients in both treatment arms. The ERG requested from the company an explanation how this estimate was calculated. In their response to the clarification letter, the company stated that the cost of standard of care was more like a nominal figure. Furthermore, the company stated that the SoC costs can be set to zero in the model with minimal impact on the ICER.[39] The ERG considers that for the SoC annual cost input for the model, rather than a nominal figure, an evidence-based figure should have been used, which is based on the expected health resource use of LD patients in the UK. In Section 6, results from the exploratory scenario analyses will be presented, where the annual cost for the SoC is varied to different values.

In the CS, it was stated that the estimated cost per patient with an abnormality was based on costs associated with an inpatient hospital stay, fraction of patients with that abnormality, and the number of lipodystrophy-related inpatient stays per patient.

The ERG requested from the company to provide details of the estimation of the abnormality costs per patient. In their response to the clarification letter, the company stated that costs per inpatient hospital stay for each organ were computed using the Health Resource Group (HRG) currency codes on Table 35, which yielded values of £11,888 for heart, £16,556 for kidney, £22,104 for liver, and £1,301 for pancreas abnormality.[39] However, it was still not clear to the ERG, how these values were derived from the HRGs.

Similar to the organ impairment associated disutility calculations explained in Section 5.3.3.7, the ERG identified the same programming errors while calculating the expected costs caused by the organ impairments. These errors will be corrected and the impact of the correction of programming errors (and using alternative formulae) will be explored in Section 6 of this report.

The company stated that no costs were included for hyperphagia, PCOS, inability to perform school or work, impaired physical appearance, or abnormal laboratory levels, because costs for these attributes were hard to quantify and varied substantially. Furthermore, the company argued, based on the NIH follow-up study, that these attributes were more likely to occur prior to metreleptin treatment than after metreleptin treatment. Therefore, setting the costs equal to £0 was deemed to be conservative.

It is a limitation that these costs were not included and no estimate was provided from the observed resource use from the literature or NIH follow-up study or other studies. However, the impact of ignoring these costs seems to have negligible impact on incremental costs. In Section 6, results from the exploratory scenario analyses will be presented, where these attribute costs are varied to different values.

Since a large number of assumptions and data were based on the expert opinion from two clinical advisors who treat lipodystrophy at Addenbrooke's Hospital, the ERG asked the company to provide all details of the communication between the company and these clinical experts. Furthermore, details on the justifications for clinical assumptions used in the model were requested. However, very little information on these requested items was provided by the company to the ERG. Therefore, the validity of some assumptions remains unclear.

The only adverse event costs to be incorporated in the analyses were those of hypoglycaemia. Other treatment emergent adverse events, such as fatigue, neutralising antibodies, injection site issues, and weight decrease were not deemed likely to have a large impact on the cost-effectiveness analysis by the company. It is likely that AEs like fatigue, neutralising antibodies, and injection site issues involve a certain amount of adverse event costs. The ERG is of the opinion that, although the impact of these AEs on the cost-effectiveness analysis can be marginal, the costs related to these AEs should have been included in the model, for completeness.

5.3.4 Model evaluation

The results of the health economic analysis are presented in terms of the incremental QALYs and incremental costs for metreleptin versus standard of care. The CS also included the results of the deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA). In the PSA, alternative parameter values were simulated while not varying the set of patients included in the model. The following groups of parameters were sampled in the PSA:

- Costs of treatment
- Utility decrements of lipodystrophy-related complications
- Organ abnormality transition probabilities
- Discontinuation rate
- Probability estimates for number of organ abnormalities
- Discount rate

For the PSA, a value of 25% of the base value of the parameters was used as the standard error of many of the parameters, since many parameter inputs were not from taken from literature or estimated from clinical data, but assumption-based. In addition to the PSA, the results of a number of deterministic one-way and multi-way sensitivity analyses and scenario analyses were also presented in the CS (see Box 2).

Box 2: Sensitivity and scenario analyses presented within the CS

Deterministic one-way sensitivity analyses

- Utility decrements
- Annual cost of lipodystrophy-related complications
- Annual treatment costs per patient
- Model specifications
    - Discount rate costs
    - Discount rate life years and QALYs
    - Annual medical cost increase
    - Annual pharmacy cost increase
- Organ progression probabilities
- Relationship between organ abnormality and survival
- Time horizon of 30 years

Deterministic multi-way sensitivity analyses

- Assumes a lower price for metreleptin
- Doubles the hyperphagia utility decrement
- Incorporates resolution of heart abnormalities for some patients who experience a resolution of hypertension

Scenario analyses

- Future price changes
- Reduced initial price
- Elimination of mortality benefit of metreleptin for PL patients
- Changes to assumptions regarding organ abnormality progression
- Alternate survival extrapolation methods
- Earlier treatment initiation

ERG comment:

The company, in its response to the clarification letter, submitted an updated electronic model. The following changes were implemented to the original model in the updated version.

- A longer time horizon was used (90 years instead of 60 years)
- A mortality cap is implemented, which will take the corresponding age and gender adjusted mortality figure from the general UK population, if the survival estimate for a GL or PL patient generates a lower mortality estimate (hence LD patients will always have higher mortality than the UK general population)
- Transition probabilities for organ impairment were changed for both metreleptin arm and SoC arm patients due to the updates of the data from the NIH Follow-up study as well as the change of the matching method used (organ impairment progression probabilities estimated for the metreleptin and SoC arms from both the original and the updated models are given in Table 37 below).

- The imputation approach for the hyperphagia was updated. Previously in the original model, if there was no real-world data on hyperphagia in the second visit (during which hyperphagia was assessed), it was assumed that the patient had no hyperphagia. In the original model, if there is no real-world data, the patient is assumed to have a 9% probability of having hyperphagia (average baseline incidence of hyperphagia in the NIH Follow-up study).
- Some of the PSA and DSA settings were adjusted (upper and lower bounds for the metreleptin drug acquisition costs and the clinical inputs from the NIH follow-up and GL/PL natural history studies were updated, and the transition probabilities were sampled from Beta distribution in the new version, in comparison to the Normal distribution in the previous version)

Table 37: The estimated organ impairment progression probabilities in the original and in the updated versions in the electronic model

Estimated progression probabilities for the updated model - NIH Follow-up study updated data			
Progression event	**Estimated progression probability**	**Number of patients at risk**	**Number of progressions**
0 to 1	0.0393	2	1
1 to 2	0.0555	14	4
2 to 3	0.0652	44	20
3 to 4	0.0219	52	5
Estimated progression probabilities for the original model - NIH Follow-up study original data			
Progression event	**Estimated progression probability**	**Number of patients at risk**	**Number of progressions**
0 to 1	0.054	4	1
1 to 2	0.050	13	5
2 to 3	0.083	47	17
3 to 4	0.039	48	7
Estimated progression probabilities for the updated model - Matched GL/PL Natural History Patients (using Mahalanobis matching)			
Progression event	**Estimated progression probability**	**Number of patients at risk**	**Number of progressions**
0 to 1	0.0896	33	33
1 to 2	0.1305	41	35
2 to 3	0.0860	36	22
3 to 4	0.0047	22	4

Estimated progression probabilities for the original model - Matched GL/PL Natural History Patients (N=47)			
Progression event	**Estimated progression probability**	**Number of patients at risk**	**Number of progressions**
0 to 1	0.089	36	36
1 to 2	0.173	42	39
2 to 3	0.123	44	36
3 to 4	0.062	36	16
Sources from top to the bottom: from Table 71 from the CS; Table 7 from the second tier of the response to the clarification letter; from Table 78 from the CS and Table 9 from the second tier of the response to the clarification letter.[1, 39]			

It should be noted that in the updated electronic model, for the SoC arm, the ERG noticed that the company used the wrong transition probability for estimating the risk of developing the 4th organ impairment. Instead of using 0.47% obtained from the matched untreated population from the GL/PL natural history study, the company used the estimate for the metreleptin patients from the NIH follow-up study (2.19%) in the model.

Furthermore, the ERG identified another programming error, which affected the company submission base-case. Due to the eligibility criteria of the original expected licensed indication, the company should have taken severe PL patients with triglycerides > 500 mmol/l and/or HbA_{1c} > 8% into account. However, the company applied the thresholds in a wrong way and applied these minimum thresholds as maximum thresholds. This wrong implementation of the license indication had excluded several severe PL patients from the base-case analysis. The ERG corrected these errors and present the corrected CS base-case analyses in Section 6.

5.4 Headline results reported within the company's submission

This section summarises the results of the economic analyses as presented by the company in its latest response to the clarification letter with the updated electronic model.[39] The company considered four different base case scenarios depending on the size of the vial and the price used for metreleptin. Thus, the results of the first base case scenario (BC1) are based on metreleptin list price and on a 10 mg vial size, which is currently being considered for marketing authorisation. However, it is expected that vials of 2.5 mg, 5 mg and 10 mg will be approved within three months after marketing authorisation. Therefore, the results of the second base case scenario (BC2) are based on metreleptin list price and on all available vial sizes. The results of the third and fourth base case scenarios (BC3 and BC4) are obtained from BC1 and BC2 after applying a [redacted]PAS price discount to metreleptin since the company expects this to be approved by PASLU.

5.4.1 Headline total QALYs and total costs for metreleptin versus standard care

Table 38 summarises the results of the economic analyses conducted for the four base case scenarios described above. Note that only discounted results are presented and that the difference in scenarios is only on the costs side of the analysis.

Table 38: Summary economic analyses results – company base case scenarios (discounted)

	LYs	QALYs	Costs BC1	Costs BC2	Costs BC3	Costs BC4
Metreleptin	18.36	8.56	£11,014,034	£5,652,808	[redacted]	[redacted]
SoC	14.71	0.25	£67,809	£67,809	£67,809	£67,809
Incremental	3.65	8.31	£10,946,226	£5,585,000	[redacted]	[redacted]
ICER	--	--	£1,316,932/ QALY	£671,927/ QALY	[redacted]/ QALY	[redacted]/ QALY

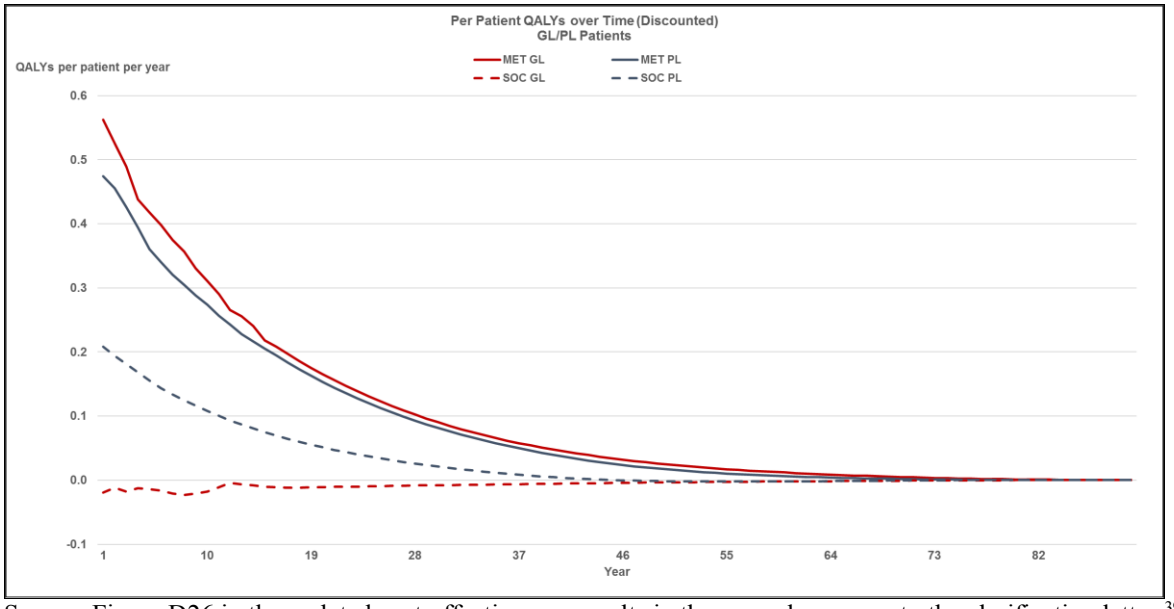
Sources: Table D44, D45 in the updated cost-effectiveness results in the second response to the clarification letter and Table 3 and 4 in the updated PAS submission template in the second response to the clarification letter.[39]

BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.

Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

In all scenarios, more than 99% of the total costs for the metreleptin arm are due to the cost of the therapy. Other medical costs are £26,156 in the four scenarios (less than 1% of the total costs). In the standard of care arm 65% of the total costs are due to therapy and 35% due to other medical costs. Life years and QALYs are accrued over a time horizon of 90 years. On average, metreleptin resulted in 39.04 (undiscounted) life years and 16.52 QALYs, whereas the standard of care arm resulted in 28.79 life years but negative (-0.19) QALYs. After discounting was applied, metreleptin resulted in 18.36 life years and 8.56 QALYs, and the standard of care arm resulted in 14.71 life years and 0.25 QALYs. The distribution of the QALYs per patient per year for both treatment arms and PL and GL patients separately is presented in Figure 7. In particular, this figure shows that for GL patients in the SoC arm the number of QALYs per year are always negative or zero suggesting that (from the general public point of view) these patients would rather die (at any time) than living with the disease.

Figure 7: QALYs per patient per year for metreleptin and SoC for PL and GL patients



Source: Figure D26 in the updated cost-effectiveness results in the second response to the clarification letter.[39]

ERG comment:
Results are generally well presented, although a discussion of the main results is missing in the company submission. In particular, the ERG considers that the face validity of the results regarding LYs and QALYs gained should have been explored. As mentioned in Section 5.3 of this report, the ERG has serious concerns about the validity of the QALYs presented by the company. Despite the significant amount of (undiscounted) life years predicted by the model in both arms, the number of QALYs was relatively low, especially in the SoC arm, which this was close to zero (or even negative when no discount was applied). Although the limitations of the study by Dhankar et al. 2015 were also discussed in Section 5.3 of this report,[31] this paper represents the only relevant source of utilities reported by the company. A naïve calculation using the average estimated EQ-5D score in Dhankar et al. (0.67) and the life years predicted by the company for the SoC arm would result in 19.29 and 9.86 undiscounted and discounted QALYs, respectively. These values are completely different to those presented by the company. Additional scenarios on utilities were explored by the ERG, and their results will be presented in Section 6 of this report.

Note that the ERG identified programming errors in the company base-case analyses, which are corrected and the impact of the corrections on cost-effectiveness of metreleptin is presented in Section 6.

5.4.2 Sensitivity analyses presented within the company's submission

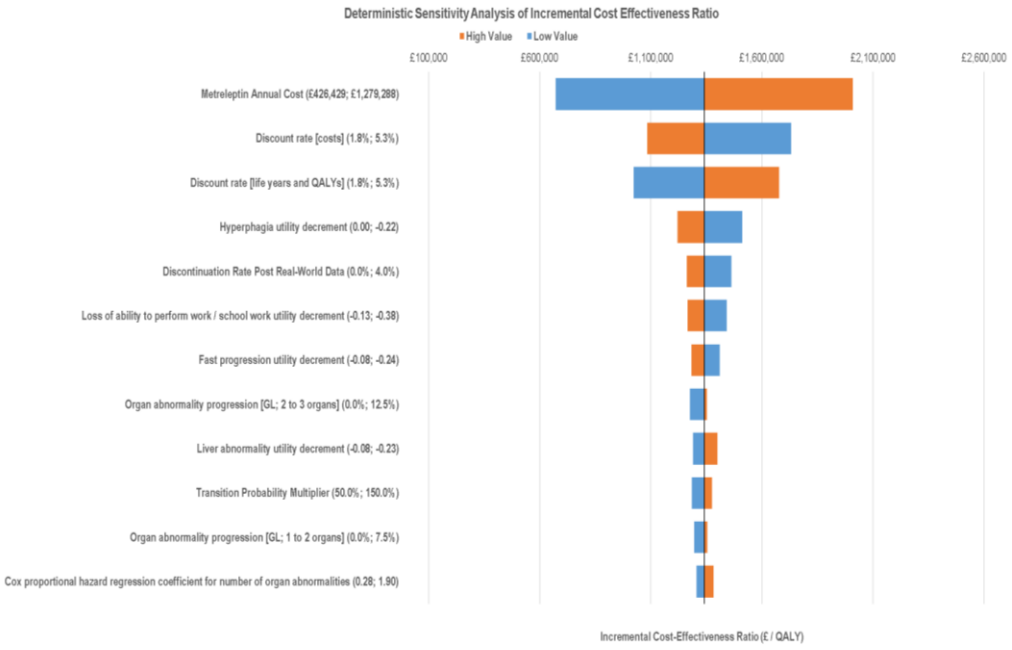
The company conducted a number of sensitivity, scenario a subgroup analyses. The results of all these analyses are summarised below. Only discounted results are presented here.

5.4.2.1 Sensitivity analyses

Sensitivity analyses included deterministic (DSA) and probabilistic sensitivity analyses (PSA). Univariate sensitivity analysis was performed on all single parameters of the model.

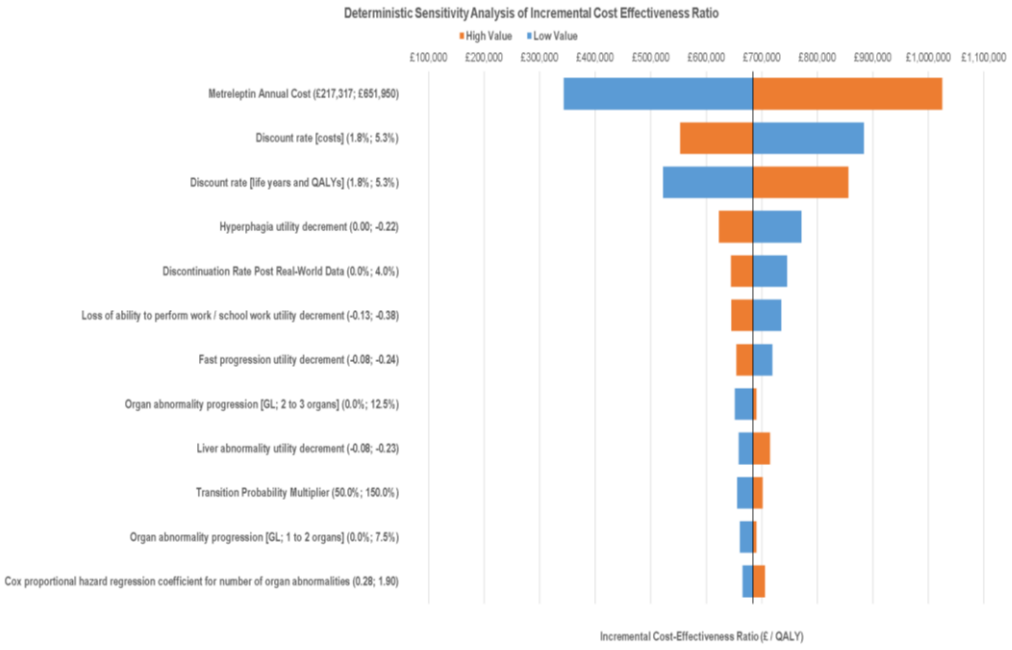
The results of the univariate DSAs were presented by the company as tornado diagrams and they are shown (for the four base case scenarios mentioned above) in the figures below. It was observed that in the four base case scenarios the metreleptin annual cost and the discount rates were the parameters for which the ICER was most sensitive. However, it should be noted that these parameters are typically not included in a DSA since they refer to structural/methodological uncertainty rather than parameter uncertainty. Besides these, the ICER was most sensitive to changes in the utility decrement due to hyperphagia and discontinuation rate.

Figure 8: Tornado diagram for BC1 – metreleptin list price and 10 mg vial size



Source: Figure D29 in the updated cost-effectiveness results in the second response to the clarification letter.[39]

Figure 9: Tornado diagram for BC2 – metreleptin list price and multiple vial sizes



Source: Figure D30 in the updated cost-effectiveness results in the second response to the clarification letter.[39]

Figure 10: Tornado diagram for BC3 – metreleptin PAS price and 10 mg vial size

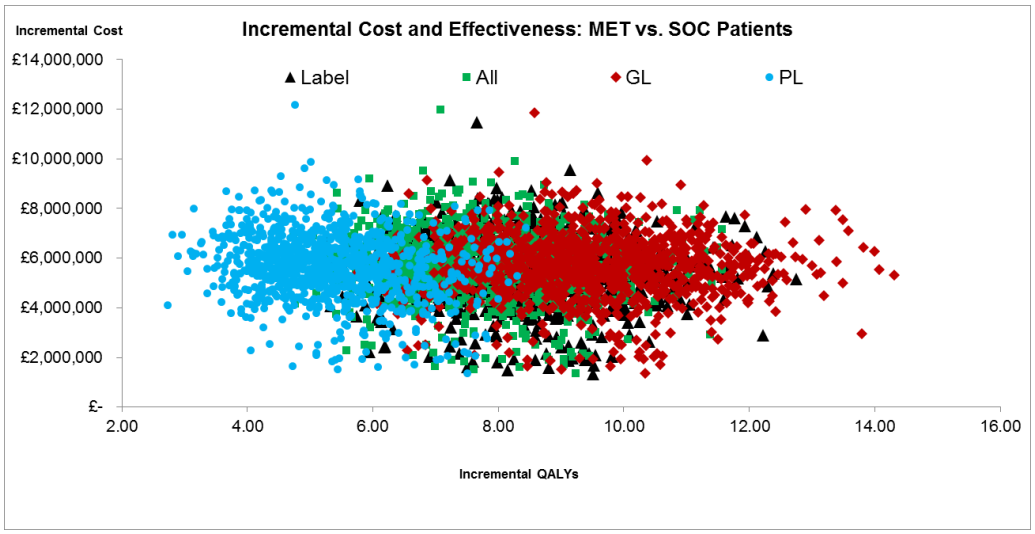
Source: Figure 1 in the updated PAS submission template in the second response to the clarification letter.[39]

Figure 11: Tornado diagram for BC4 – metreleptin PAS price and multiple vial sizes

Source: Figure 2 in the updated PAS submission template in the second response to the clarification letter.[39]

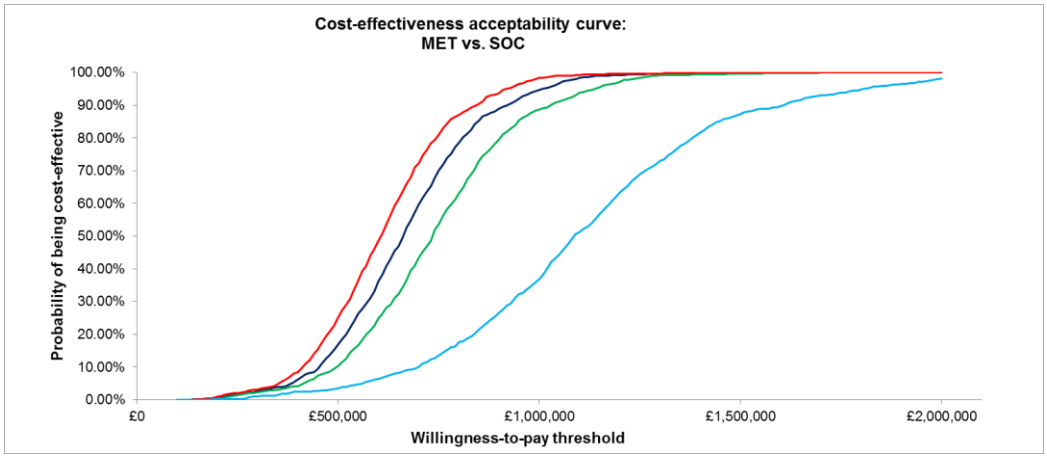
PSA was conducted using 1,000 model runs. The company presented results of the PSA as scatter plots of the total incremental costs and incremental QALYs on the CE plane and as cost effectiveness acceptability curves (CEACs). The PSA results were presented by the company for BC2 and BC4 only. The results of the two scenarios are presented in the figures below. Note that for BC1 and BC3, the only difference is on the cost side compared to BC2 and BC4. Therefore, the shape of the scatter plot of the PSA outcomes for BC2 and BC4 would be the same as that in BC2 and BC4, respectively, but shifted up on the incremental cost (Y) axis, which would result in less favourable CEACs for metreleptin.

Figure 12: PSA results on the CE plane – BC2: metreleptin list price and multiple vial sizes



Source: Figure 31 in the updated cost-effectiveness results in the second response to the clarification letter.[39]

Figure 13: CEACs – BC2: metreleptin list price and multiple vial sizes



Source: Figure 32 in the updated cost-effectiveness results in the second response to the clarification letter.[39]

Figure 14: PSA results on the CE plane – BC4: metreleptin PAS price and multiple vial sizes

Source: Figure 3 in the updated PAS submission template in the second response to the clarification letter.[39]

Figure 15: CEACs – BC4: metreleptin PAS price and multiple vial sizes

Source: Figure 4 in the updated PAS submission template in the second response to the clarification letter.[39]

ERG comment:

As in the base case analyses, the CS did not provide any interpretation of the results of the sensitivity analyses.

Parameters like time horizon, discount rates or the treatment costs are usually not included in the sensitivity analyses. The impact of changing these parameters on the ICER is usually assessed in scenario analyses. This is the approach followed by the ERG when presenting the results of their own analyses. In response to the clarification letter, the company indicated that the metreleptin cost per patient was included in the sensitivity analyses due to the uncertainty about the average per patient dose. However, the ERG considers that metreleptin cost should

not be explored in sensitivity analyses. If there are factors that impact annual metreleptin acquisition costs (such as patient dose), they should be varied independently from metreleptin price. In the updated version of the model submitted with the response to the clarification letter, the company did not include the time horizon in the sensitivity analyses as requested by the ERG. However, the discount rates were still included in the DSA and PSA. The analyses conducted by the ERG considered the discount rates fixed to 3.5% for both costs and effects.

The ERG found it unclear how the upper and lower limits for the parameters included in the DSA were obtained. The company indicated in the response to the clarification letter that since many parameters were assumption-based, ranges were selected to illustrate a wide set of reasonable values and that the bounds were updated to more clearly reflect the source of uncertainty. However, the ERG considers this still unclear since no discussion on the validity of these limits was provided. For those parameters that were derived from analysis of the NIH follow-up or natural history data, the updated version of the model included 95% CI limits in the DSA and the PSA. The ERG agrees with this latter choice. The ERG also identified some implausible values for some input parameters (e.g. negative standard deviations) and inappropriate probability distributions assigned to some parameters (e.g. normal distribution for disease progression or discontinuation rates, which might lead to negative estimates). The company corrected this in the updated version of the model.

PSA results were presented as scatter plots of total incremental costs and QALYs in the CE plane and CEACs with no further explanation. It is unclear why four different subgroups were presented in the CE plane and CEACs, as this was not the approach used in the base case scenarios or the DSAs. This makes the interpretation of the results more difficult.

5.4.2.2 Scenario analyses

The results of the scenarios run by company are shown in Table 39.

Table 39: Scenario analyses results

Scenario	Assumptions	QALYs gained	ICER BC1	ICER BC2	ICER BC3	ICER BC4
Base case	List price, with multiple vial sizes	8.31	£1,316,932	£671,927	[redacted]	[redacted]
Base case plus assume [redacted] lower price for Metreleptin	List price with [redacted] discount, with multiple vial sizes	8.31	[redacted]	[redacted]	--	--
Base case plus alternate inputs	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension	9.78	£1,132,896	£577,988	--	--
Base case plus alternative inputs assume [redacted] lower price for Metreleptin	List price with [redacted] discount, with multiple vial sizes, doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension	9.78	[redacted]	[redacted]	[redacted]	[redacted]
Future Price Changes: Loss of Metreleptin exclusivity	Metreleptin list price falls 90% after 10 years	8.31	£731,131	£373,391	[redacted]	[redacted]
Elimination of mortality benefit of Metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ abnormality.	8.31	£1,321,485	£674,235	[redacted]	[redacted]
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	8.03	£1,346,604	£687,076	[redacted]	[redacted]
	all organ progression probabilities decreased by 50%	8.68	£1,276,347	£651,156	[redacted]	[redacted]
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	8.26	£1,326,825	£676,952	[redacted]	[redacted]

Scenario	Assumptions	QALYs gained	ICER BC1	ICER BC2	ICER BC3	ICER BC4
Alternate survival extrapolation methods: GL curve parameterisation	Weibull	8.67	£1,292,851	£659,609	[redacted]	[redacted]
	Log Normal	8.52	£1,302,991	£664,820	[redacted]	[redacted]
	Logit	8.32	£1,315,472	£671,192	[redacted]	[redacted]
Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	8.42	£1,276,963	£651,353	[redacted]	[redacted]
	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	8.07	£1,360,883	£694,567	[redacted]	[redacted]
Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	8.28	£1,266,105	£646,143	[redacted]	[redacted]
Early treatment initiation at age 1 (CGL)	List price, multiple vial sizes	12.35	--	£865,667	[redacted]	[redacted]
Early treatment initiation at age 1 (CGL) plus alternate inputs	List price, multiple vial sizes plus double hyperphagia decrement, plus parental disutility of -0.05 per period	14.51	--	£736,750	[redacted]	[redacted]

Sources: Table D51, D52 in the updated cost-effectiveness results in the second response to the clarification letter and Table 5 and 6 in the updated PAS submission template in the second response to the clarification letter.[39]
BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.
Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

ERG comment:
In general, the ICER is rather stable across all scenarios (per base case). The lowest ICER ([redacted]) was found for the scenario with [redacted] discount on metreleptin list price, assuming multiple vial sizes, doubled hyperphagia disutility and incorporating heart abnormality improvement measured by hypertension. The company argued that this scenario reflected the true metreleptin benefit. However, the ERG does not agree with that statement because there is no evidence that hyperphagia disutility should be twice as high from its DCE study estimate and also the argument that hypertension improvement is a surrogate for heart organ abnormality is deemed to be not convincing by the ERG.

5.4.2.3 Subgroups analyses

The following four subgroups were included in the economic analyses: generalised lipodystrophy (GL) patients (including those who do not meet the labelled indication), partial lipodystrophy (PL) patients (including those who do not meet the labelled indication), all NIH patients (including those who do not meet the labelled indication) and congenital generalised lipodystrophy (CGL) patients (including those who do not meet the labelled indication). A detailed description of these subgroups can be found in Section 2.2 of this report. The subgroup analyses were conducted by selecting the model results from those patients who meet the subgroup criteria. Discounted results are presented in Table 40.

Table 40: Summary results of the company subgroup analyses (discounted)

Subgroup	Number of patients	LYs		QALYs		ICER BC1	ICER BC2	ICER BC3	ICER BC4
		MET	SoC	MET	SoC				
All NIH	112	19.31	16.39	8.42	0.74	£1,469,868	£749,758	[redacted]	[redacted]
GL	68	17.98	13.61	8.87	-0.52	£1,202,792	£613,793	[redacted]	[redacted]
PL	44	21.37	20.68	7.73	2.68	£2,237,881	£1,140,745	[redacted]	[redacted]
CGL	48	19.27	14.77	9.57	-0.91	£1,170,263	£597,107	[redacted]	[redacted]

Sources: Table D54 (BC1), D56 (BC2) in the updated cost-effectiveness results in the second response to the clarification letter and economic model (BC3 and BC4).[39]
BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.
Abbreviations: BC = base case, CGL = congenital generalised lipodystrophy, GL = generalised lipodystrophy, ICER = incremental cost-effectiveness ratio, LYs = life-years, MET = Metreleptin, NIH = National Institute of Health, PL = partial lipodystrophy, QALYs = quality-adjusted life years, SoC = standard of care

ERG comment:
The subgroups are in line with the scope of the NICE.[27] Subgroup analysis results show that the lowest ICER was obtained for the CGL subgroup, which is also very similar to the ICER for the GL subgroup. The highest ICER was found for the PL subgroup, which approximately doubled the ICER for the CGL subgroup.

In all subgroup analysis, for each subgroup, the average results of the patients that fall into the corresponding subgroup are calculated. This approach assumes that there is no difference in terms of transition probabilities (for disease progression or survival), health care resource utilisation and utilities among all subgroups. The ERG asked the company to check the plausibility of this assumption based on the patient level data from the NIH follow-up and natural history studies. Due to the small size of both the NIH follow-up study (n=112) and the natural history study (N=178), the company deemed not feasible to estimate transition probabilities (and hazard ratios) for each subgroup. Survival however was significantly different for GL and PL patients. Therefore, survival curves and the mortality hazard ratio associated with organ abnormalities was were estimated separately for GL and PL patients. The company considered that organ abnormality progression in the natural history study was not associated with lipodystrophy sub-type, in particular after an initial organ abnormality was observed. Thus, the company consider it plausible to use a single set of transition probabilities for both groups. Nevertheless, the company's model is set up to accommodate different transition probabilities for GL and PL. Hence, the impact of this assumption on the model results could be tested, should additional data become available in the future.

5.4.3 Validation

The whole of Section 12.7 (Validation) in the CS (CS, page 190) is the following sentence: "The approach to the model has been validated with leading lipodystrophy clinical experts including Dr. Rebecca Brown, Dr. David Savage and Dr. Anna Stears, and additional meetings to review findings are underway."[1] This sentence is provided under the company submission template heading "12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections". The ERG requested that the company provide all details of the validation methods, using the AdvisHE validation tool.[93] In the response to the clarification letter,[39] the company stated that the validation exercise reported in Section 12.7 of the CS specially involved discussing the conceptual mode, assumptions, and inputs with the clinical experts. Additional validation efforts were also completed, which were reported in the AdvisHE template submitted with the response to the clarification letter. However, not all types of validation were feasible due to the rare nature of lipodystrophy and lack of prior cost effectiveness analyses.

ERG comment:
The model was validated with leading lipodystrophy clinical experts and the validation tool was completed in response to the request for clarification. However, the ERG has some concerns regarding the model validation. With respect to face validity, the company stated that experts were asked to judge the appropriateness of the conceptual model, the input data, and

the model outcomes. However, the findings of the clinical experts were not reported. Furthermore, in Section 12.5.2 of the CS (CS, page178),[1] the company stated: "The outcomes from the model were not compared with the clinical trial results as no randomised controlled trial of Metreleptin in lipodystrophy patients has been conducted, largely due to the extreme rarity and severity of the condition". Thus, cross validation was not possible, as lipodystrophy is a rare disease and there are no existing cost effectiveness models.

Although the company provided more details of the validation of the model, most parts of the completed AdvisHE document were vague and not transparent. Therefore, the validation section is clearly inadequate.

5.5 Discussion of the available evidence relating to value for money for the NHS and PSS

This chapter focuses on the economic evidence about metreleptin for the treatment of LD syndromes, submitted to NICE by the company. The analysis from the company is a QALY-based cost effectiveness model comparing metreleptin versus SoC. In BC1 (metreleptin list price and 10 mg vial size), metreleptin is expected to result in 16.71 additional QALYs compared to SoC. The undiscounted incremental cost of metreleptin versus SoC is estimated to be £19,923,178 per patient. When discounted at a rate of 3.5%, the estimated QALYs gained were 8.31 for metreleptin treatment versus SoC. The discounted incremental cost of metreleptin versus SoC was £10,946,226 per patient, yielding an ICER of £1.3Million per QALY gained. The [redacted] ICER was reported for BC4 (metreleptin PAS price and multiple vial sizes), at [redacted] per QALY gained.

Several major problems relating to the company's submission were identified by the ERG. One of the most important concerns relates to the estimation of organ impairment progression. In the analysis, the type of affected organ and the severity of an organ abnormality were not taken into account. Organ impairment improvements were only considered for metreleptin treatment and organ impairment progression in the SoC arm was overestimated by the use of a staggering approach. Furthermore, the approaches used to incorporate time to event data from the NIH follow-up study and from the GL/PL natural history study were incompatible. The simulated number of impaired organs was biased in favour of metreleptin by use of an implausible formula in the electronic model. In addition, patient characteristics had no impact on the transition probabilities for the number of impaired organs. Due to the issues outlined above, the ERG has substantial concerns about the appropriateness of the statistical methods used by the company. In order to address these concerns, the ERG requested that the company conduct de novo statistical analysis, using more generally accepted methods in line with the guidance provided in NICE DSU TSD 17,[90] however, the company stated that they were not able to finalise this request given the timelines.

There are also serious concerns surrounding the survival analyses conducted by the company and the implementation of these analyses in the model. The estimation and extrapolation of the survival analyses from different datasets results in inconsistencies. There is also a lack of face validity for the survival extrapolation as the survival model estimates that after 65 years, over 23% of the patients are still alive. Considering that the average baseline age was 24 years, these survival estimates might not be valid for LD patient population. Survival is extrapolated by a

function based only on age, gender, type of lipodystrophy, and number of organs impaired, and it is questionable whether this is the most plausible survival function and whether other important covariates were missed.

The ERG identified several issues related to the matching methodology. The first issue is about the appropriateness of the company's approach to the use of data to inform the estimates of treatment effectiveness. Moreover, there is a lack of clarity regarding the matching algorithm used by the company. The ERG also had problems with the independent estimation of the organ impairment transition probabilities from the treated and the matched untreated patient datasets. Furthermore, insufficient interpretation of the matching results was provided.

There are also several issues identified by the ERG, which relate to the extrapolation of blood-lab measures (HbA_{1c} and triglycerides) and other attributes not related to organ damage conducted by the company in the model. Furthermore, while metreleptin discontinuation is only applied for organ impairment, the impact of discontinuation is not reflected in other disease attributes, which creates a bias in favour of metreleptin.

The ERG has several vital concerns about the derivation of the utility decrement from the company's DCE. The key issue is that the use of DCE to directly obtain disutility values for heath states is still in its infancy. The most striking unresolved methodological issue relates to the fact that DCE classifies health states far more often below zero than TTO and produces lower average health state values. This was indeed observed in the results of the current DCE study. In addition, various major flaws in the design of the DCE and the analysis of the data were identified, hence, the ERG considers the disutility weights presented by the company as speculative.

There are also a few issues related to resource use and costs included in the model, which lead to incompleteness of the model.

Finally, the ERG also has concerns about the sensitivity analyses and the validation of the model. Parameters like treatment costs and discount rates were included in the sensitivity analysis, although these parameters are usually not included in a DSA. It was unclear why the PSA results are presented in four different subgroups. The ERG considered the validation of the model to be inadequate and the information provided about the validation to be very vague and not transparent.

Given the level of evidence submitted by the company, it proved impossible for the ERG to give an indication on the cost-effectiveness of metreleptin. The CE model is based on non-reliable evidence and unjustified assumptions. More specifically, the RWD data used to estimate important inputs for the model is not reliable (e.g. twice data updates without being able to track what was been updated and how, vague definitions of organ impairment were applied). Additionally, both the methods used in quantifying the treatment effect and the DCE methodology used were not transparently reported but more importantly not credible.

The next chapter outlines the additional analyses conducted by the ERG, with the aim of addressing some of the problems identified in the critical appraisal of the economic analysis.

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Introduction

In this chapter the additional analyses performed by the ERG are presented. As described in Chapter 5, the ERG identified some programming errors in the model and some critical issues related to the input evidence used in populating the company's model.

First, the results are presented of a re-analysis of the company's economic analysis base-cases, following the correction of technical programming errors by the ERG.

Next, the results of several exploratory scenario analyses done by the ERG to explore areas of uncertainty will be presented.

6.2 Re-analysis of the company's economic analysis following the correction of technical programming errors

The ERG identified the following errors in the company model:

- Wrong transition probability is used for the fourth organ impairment annual probability for SoC
- The minimum HbA_{1c} and triglyceride thresholds for the PL eligibility were applied as maximum thresholds for PL patients
- The costs and disutilities associated with organ impairments were wrongly calculated, and different formulae were used for SoC and metreleptin arms

The base-case model's results after correcting these errors can be seen in Table 41 below.

Table 41: Summary economic analyses results – corrected company base case scenarios (discounted)

	LYs	QALYs	Costs BC1	Costs BC2	Costs BC3	Costs BC4
Metreleptin	18.47	9.12	£11,400,639	£5,850,224	[redacted]	[redacted]
SoC	14.99	0.43	£66,712	£66,712	£66,712	£66,712
Incremental	3.48	8.68	£11,333,927	£5,783,512	[redacted]	[redacted]
ICER	--	--	£1,305,355/ QALY	£666,101/ QALY	[redacted]/ QALY	[redacted]/ QALY

BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.

Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

As observed in Table 41, these errors do not seem to have a major effect on the cost effectiveness results (comparing to the values in Table 38). The subgroup analysis with the corrected CS model can be seen in Table 42 below.

Table 42: Subgroup analyses results – corrected company base case scenarios (discounted)

Subgroup	Number of patients	LYs		QALYs		ICER BC1	ICER BC2	ICER BC3	ICER BC4
		MET	SoC	MET	SoC				
All NIH	112	19.39	16.60	9.42	1.82	£1,486,050	£758,164	[redacted]	[redacted]
GL	68	18.09	13.92	9.78	0.39	£1,203,175	£614,091	[redacted]	[redacted]
PL	44	21.40	20.74	8.87	4.03	£2,334,659	£1,190,374	[redacted]	[redacted]
CGL	48	19.40	15.16	10.70	0.05	£1,152,297	£588,002	[redacted]	[redacted]

BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.

Abbreviations: BC = base case, CGL = congenital generalised lipodystrophy, GL = generalised lipodystrophy, ICER = incremental cost-effectiveness ratio, LYs = life-years, MET = Metreleptin, NIH = National Institute of Health, PL = partial lipodystrophy, QALYs = quality-adjusted life years, SoC = standard of care

Again, the impact of the errors was relatively small. As in the company subgroup analysis, CGL patients have the largest gain in QALYs with metreleptin.

Total QALYs seem to increase in the corrected model, however incremental costs and ICERs seem to be similar. The ERG did not repeat the PSA and the DSA of the corrected model, since the results and the main findings are not expected to change substantially and the company's model is extremely slow. To explore structural and input uncertainty, the ERG conducted various scenario analyses. These scenarios are presented only for BC2 and BC4, as the impact of having/not having multiple vial sizes available on ICER is already known from the previous analyses.

6.3 Exploratory scenario analyses conducted by the ERG

The ERG conducted six additional scenario analyses to explore structural and input parameter uncertainty. These scenarios are described below:

- Scenario 1: The impact of metreleptin discontinuation was reflected in not only in organ impairment progression, but also in the progression of other disease attributes. For instance, when a patient on metreleptin discontinues the treatment, the corresponding values from the SoC arm were assumed for discontinued patients' blood-lab and other attributes (e.g. hyperphagia, ability to work, etc.)
- Scenario 2: Abandoning the logical constraint imposed on the SoC arm patients, which never allowed them to have fewer number of organ impairments than metreleptin
- Scenario 3: Assuming that there is no difference between the SoC and metreleptin treatments in terms of the disease attributes other than organ impairment and blood-lab values (e.g. hyperphagia, ability to work, physical appearance, etc.) during a patient's lifetime
- Scenario 4: Using utility input from Dhankar et al. for all the years that a patient is alive
- Scenario 5: Except for the data at baseline, no real-world data is directly used in the simulation of the organ/blood-lab attributes for the metreleptin arm patients

- Scenario 6: For the disutility and cost calculations associated with the number of organs impaired, the corrected formula from the metreleptin arm (assuming independent application of the organ specific abnormality probability weights) is used in both arms.

6.3.1 Results of the ERG's scenario analyses

The results from these exploratory scenario analyses are given in Table 43 below.

Table 43: Exploratory scenario analyses from the ERG

Scenario	Assumptions	QALYs metreleptin	QALYs SoC	QALYs gained	ICER BC2	ICER BC4
Base case	Multiple vial sizes	9.12	0.43	8.68	£666,101	[redacted]
Scenario 1	The impact of metreleptin discontinuation in other attributes	6.78	0.43	6.34	£911,588	[redacted]
Scenario 2	Abandoning the logical constraint imposed on the SoC arm patients	9.12	0.45	8.66	£667,515	[redacted]
Scenario 3	No change between the SoC and metreleptin treatments in terms of attributes other than organ impairment and blood-lab values	2.82	0.43	2.39	£2,424,009	[redacted]
Scenario 4	Using utility input from Dhankar et al. for all the alive years of the patient	12.38	10.05	2.33	£2,480,754	[redacted]
Scenario 5	Except for the data at baseline, no real-world data is directly used in the simulation of the organ/blood-lab attributes for the metreleptin arm patients	6.53	0.45	6.08	£881,810	[redacted]
Scenario 6	Alternative organ impairment associated cost/disutility calculation	8.28	-0.43	8.71	£663,725	[redacted]

Scenarios 3 and 4 had the highest impact on the results since the ICERs in these scenarios are three-fold larger than the ICER from the base case(s).

In scenario 3, the treatment effect of metreleptin on attributes like hyperphagia, ability to work was assumed to be zero. The impact on the ICER suggests that the treatment effect of metreleptin on these attributes is one of the key drivers of the cost effectiveness. It should be noted that the evidence on the effectiveness of metreleptin for these attributes was rather weak, therefore future research can definitely reduce this uncertainty.

Since the ERG was concerned about the utility estimates provided by the company (including the overall methodological DCE approach), scenario analysis 4 demonstrated how different the utility estimates used in the submission were compared to the EQ5D values from the literature and how changing the utility input to the model can change the results substantially

6.4 Discussion

As discussed in the previous section, the ERG considers that the evidence base used in this cost effectiveness analysis is not reliable and trustworthy enough to inform decisions on metreleptin. However, the ERG expects that the decision uncertainty from the payer perspective related to metreleptin's value for money would be rather low, in view of the fact that the ICER estimates from all analyses, including the analyses with PAS discounts, are markedly above the acceptable thresholds considered for orphan drugs.

7. COST TO THE NHS AND PSS AND OTHER SECTORS

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS

The CS includes a budget impact model to estimate the total costs to the NHS, for a period of five years, of adopting metreleptin in England. Published data on the incidence and prevalence of lipodystrophy relevant to the expected metreleptin license were lacking. Since EAP data from a decade of metreleptin use in UK clinical practice were deemed relevant and representative, these data were used to estimate patient numbers for the budget impact analysis. In December 2017, there were 26 patients in the UK receiving metreleptin (nine patients with GL and 17 with uncontrolled PL). Based on expert opinion, it was assumed that yearly six new patients (two for GL and four for PL) are eligible for metreleptin treatment. For mortality, it was assumed that one patient with PL will die every year and one patient with GL will die every two years. Based on these assumptions, the number of patients treated with metreleptin will rise from 22 in year 1 to 44 in year 5. The estimated numbers of patients eligible for metreleptin treatment over the next five years are presented in Table 44.

Table 44: Estimated eligible patient numbers for metreleptin

Patient group	Year 1	Year 2	Year 3	Year 4	Year 5
GL	9	11	12	14	15
PL	17	20	23	26	29
Total	26	31	35	40	44

Source: Table D58 in the CS[1]

GL, generalised lipodystrophy; PL, partial lipodystrophy

It is assumed that the uptake rate will rise from 85% in year 1 to 90% in year 5, based on clinical expert opinion. A discontinuation rate of 0% in the first five years was assumed for metreleptin. The expected uptake rate of metreleptin is shown in Table 45.

Table 45: Expected uptake rate of metreleptin over the next five years

	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake rate	85%	85%	90%	90%	90%

Source: Table D59 in the CS[1]

The first budget impact analysis assumed the availability of only 10 mg dose vials at a list price of £2,335, resulting in annual per patient drug costs of £852,859. Since all start-up costs concerning the administration of metreleptin will be covered by Aegerion, supportive medicines costs are expected to be zero. This resulted into a net budget impact of £18,762,893 in year 1 rising to £34,114,350 in year 5 and a cumulative net budget impact over years 1-5 of £133,045,965.

In the second budget impact analysis, it is assumed that 18.23% of the patients with lipodystrophy will receive a 3 mg dose (at a list price of £583.80), 69.23% will receive a 5 mg dose (at a list price of £1,167.50), and 11.54% will receive a 10 mg dose of metreleptin. This resulted in a net budget impact of £9,561,936 in year 1 rising to £17,385,338 in year 5 and a net cumulative budget impact of £67,802,818.

In the third analysis, a PAS discount of [redacted] was assumed for 11.3 mg vial (10 mg dose). The anticipated PAS price was [redacted] per 11.3 mg vial, which equates to treatment costs of [redacted] per patient per annum. In year 1, the net budget impact was [redacted] and rising to [redacted] in year 5. The cumulative net budget impact was [redacted] for all patients with lipodystrophy.

Budget impact analysis 4 assumed the availability of all three vial sizes and a PAS discount of [redacted]. Based on EAP data, it was assumed that 11.54% of the patients with lipodystrophy receive the 10 mg dose vial, 69.23% of patients receive the 5 mg dose vial, and 19.23% of patients receive the 2.5 mg dose vial. This resulted in a net budget impact of [redacted] in year 1 and [redacted] in year 5 (net cumulative budget impact over years 1-5 was [redacted]).

7.2 ERG critique of the company's budget impact analysis

In general, the ERG considers the assumptions made in the budget impact analysis as plausible. However, there are some concerns about the expected uptake rate of metreleptin, which is assumed to rise over the next five years from 85% in year 1 to 90% in year 5. The ERG requested that the company to provide all details of data used for this assumption. The company stated that this assumption was based on company forecast assumptions. The uptake is expected to be high, but due to potential barriers, some patients may be unwilling or unable to receive metreleptin. The ERG considers the high expected uptake rate as reliable, but the reason behind the rising uptake rate from 85% in year 1 to 90% in year 5 is still unclear. Furthermore, discontinuation of metreleptin was only included to reflect mortality of LD patients. However, discontinuation due to patient preferences or clinical recommendation was considered as 0% in the first five years, because of the small estimated patient numbers in the budget impact. Since the estimated discontinuation rate is based on clinical expert opinion and no detailed information on this expert opinion was provided to the ERG, the validity of these assumptions remains unclear.

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE

8.1 Summary of cost savings estimated within the CS

8.1.1 Nature of estimates presented

The CS includes estimates of impacts of metreleptin on (i) inability to work or attend school for patients and carers; (ii) estimates of out-of-pocket costs for patients and carers including costs related to diabetes, transportation, fertility and cosmetic treatment; and (iii) other carer costs.

8.1.2 Societal costs

A substantial number of patients with lipodystrophy are affected from birth, with symptoms such as hyperphagia and organ abnormalities manifesting in childhood. Due to hyperphagia, patients may be highly constrained by food access issues, which can heavily affect their daily lives including attending school and work. In the NIH Follow-Up study, of 50 adult patients treated with metreleptin, 48% did not work of which at least 1/3 was due to lipodystrophy. Over half (59.4%) of the 64 non-adult patients treated with metreleptin had impaired school attendance.

Patients may need 24/7 supervision from carers. Carers are mostly family members, typically the mother of the patient. Of 114 patients treated with metreleptin in the NIH follow-up study, 35% had a caregiver who was not working or who was working part time due to supporting the patient. When patients were treated with metreleptin, only 7% of these patients had a caregiver who was not working or only working part time, which is a reduction of 80%.

8.1.3 Costs borne by patients

Most patients with lipodystrophy have type 2 diabetes at a very young age. Indirect costs due to diabetes are considerably high, which are to a large extent costs for the patients and their carers.[94] These costs include loss of earnings by the patients and carers. A study from the UK estimated the earnings lost at £869 to £13,841 per patient and at £1,300 to £10,960 per carer.[95]

Other out-of-pocket costs for patients and carers are costs related to transportation to the hospital. About 20% of patients with lipodystrophy will need hospitalisation in a given year. In some patients, more than five hospitalisations per year were observed.[96] Fertility treatment and cosmetic treatment are further potential costs, which are not always reimbursed by the NHS. However, the company stated that effective management of lipodystrophy, including metreleptin treatment, is expected to mitigate these costs.

Patients treated with metreleptin would typically need to visit the specialist centre at Addenbrooke's twice a year. Thus, patients will have travel costs to Addenbrooke's in Cambridge and they probably also need an overnight stay in Cambridge.

8.1.4 Other carer costs

Two different surveys have described the substantial time burden for the majority of people living with a rare disease and their carers, with 42% spending over two hours a day on caring.

[97, 98] In the NIH follow-up study, 35% of the 114 patients treated with metreleptin had one caregiver who was not working or only working part time. After metreleptin treatment, only 7% of the patients had a carer not working or only working part time. Data about time spent on informal care by family members for patients with lipodystrophy are currently lacking. However, the company states that it is currently conducting market research in England to further understand the impact on caregivers in more detail.

8.1.5 Discussion of wider societal (non-health) benefits

A number of issues regarding the impact of metreleptin beyond direct health benefits are mentioned in the submission. However, no costs associated with inability to work or attend school were calculated in the analyses. The company admits that these attributes may impose costs, though the costs vary substantially and are hard to quantify. Furthermore, these attributes are more likely to be present in patients who receive standard of care. Therefore, the company considered including £0 in associated costs to be a conservative approach. The ERG requested that the company justify the plausibility of these assumptions. The company responded that very limited information is available about the economic burden of lipodystrophy. Moreover, the costs associated with these attributes are likely to be highly variable. As part of the NIH follow-up study, data about the extent to which patients experience each of these attributes prior and after metreleptin treatment were collected.[39] The ERG does not understand that, while there were data collected on these attributes, it was not possible to estimate associated costs. Although these attributes are more likely to be present in patients not treated with metreleptin, these attributes could still be present in some patients treated with metreleptin.

The ERG requested that the company provide more details and the source of the hospitalisation figures (20% of lipodystrophy patients are hospitalised at least once a year, with some hospitalised more than five times a year). However, the company did not respond to this request. Furthermore, the ERG has a problem with the assertion in which the company stated that metreleptin will mitigate the costs of hospitalisation and fertility and cosmetic treatment, since this is not based on any evidence.

No indirect health care costs, due to additional life-years after receiving metreleptin, were reported in the CS. The company was requested to provide estimates for these costs. The company responded that the model was not designed to include these costs. Furthermore, it was not expected that any indirect health care costs would influence the cost effectiveness results. Although the company expects the indirect health care costs due to additional life-years to be low, these costs should be included in the model for completeness.

The estimates related to informal caregivers were obtained from the NIH follow-up study. It was stated that there were 114 LD patients in the NIH follow-up study, however, this does not match any of the numbers in the studies reported elsewhere in the CS. A substantial number of informal caregivers (family members of the patient) does not work or work part time due to taking care of the patient with lipodystrophy before metreleptin treatment. After metreleptin, 7% of these caregivers are still not working or are working part time. The CS does not include costs related to informal care and productivity loss for the caregiver. Although the company states that it is currently conducting research to gain more details of these issues, the ERG

considers it as inadequate that the impact of lipodystrophy on informal carers was not identified prior to the CS.

8.2 Staffing and infrastructure requirements associated with the use of the technology

The company stated that, since metreleptin has been available for over 10 years in the UK through the EAP, there is already a lot of expertise within the NHS to support the safe and effective use of metreleptin treatment. Healthcare professionals are training the patients on the proper use of subcutaneous injections, through which metreleptin could be administered at home by the patient or carer.

Furthermore, it was stated in the CS that no additional facilities, technology, or infrastructure will be required for the introduction of metreleptin treatment on the NHS in England.

9. DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

Single arm, observation studies of metreleptin treatment found improvements in metabolic abnormalities from baseline to month 12 of treatment in patients with GL and in the subgroup of patients with PL who had similar metabolic disturbances to those seen in patients with GL (PL patients with leptin level <12 ng/ml with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L).

- In study NIH 991265/20010769, mean actual change in HbA_{1c} to Month 12/LOCF was -2.2% ($p<0.001$) for GL patients and -0.9% ($p<0.001$) for patients in the PL subgroup.[1, 37]
- In study FHA101, mean actual change from baseline to Month 12/LOCF for HbA_{1c} was -1.2% for GL patients and -0.8% for patients in the PL subgroup.[1, 38]
- In study NIH 991265/20010769, mean percent change in triglycerides to Month 12/LOCF was -32.1% ($p=0.001$) for the GL group and -37.4% ($p<0.001$) in the PL subgroup excluding the 1 outlying noncompliant patient.[1, 37]
- In study FHA101, mean percent change from baseline to Month 12/LOCF for triglycerides was similar in the GL group as -26.9%; however, for the PL subgroup, the mean percent change was lower at -8.5%. Five of the 7 patients in the PL subgroup in this study showed reductions from baseline to Month 12/LOCF in triglycerides ranging from -5.7% to -52.3%.[1, 38]

Mixed model repeated measures (MMRM) analyses indicate that these effects persist to month 36; LS mean percent changes from baseline in HbA_{1c} were -2.3%, -2.1% and -1.5% at Months 12, 24 and 36, respectively.[1, 37] The overall MMRM analysis showed a statistically significant decrease from baseline for GL patients with an LS mean change of -1.4% ($p<0.001$). Results were similar in the PL subgroup with LS mean changes in HbA_{1c} of -0.9%, -1.3%, and -1.0% at Months 12, 24, and 36 and an overall LS mean change of -0.6% ($p<0.001$).[1, 37] In the GL group, LS mean percent changes from baseline in triglycerides were -48.3%, -22.6% and -40.6% at Months 12, 24, and 36, respectively; based on the overall MMRM analysis, the LS mean change in triglycerides was -22.4% ($p<0.001$). For the PL subgroup (excluding data from the 'outlier' patient described previously), LS mean percent changes in triglycerides were -36.2%, -31.7%, and -13.7% at Months 12, 24 and 36, respectively, with an overall LS mean change of -18.6% ($p=0.004$).[1, 37]

With respect to safety and adverse events, the CS concludes that the known side effects of metreleptin can be managed as part of the normal clinical practice for patients with this complex condition. The CS does not report the safety concerns as highlighted in the Centre for Drug Evaluation and Research Report (not included in the CS) or the associated REMS.[75] The summary of safety in this report states: 'The principal safety concerns with metreleptin are T-cell lymphoma and anti-metreleptin antibodies with neutralizing activity. These concerns are of sufficient magnitude to require REMS. Other safety findings that warrant inclusion in the Warning and Precautions section of the metreleptin labelling include hypoglycemia, autoimmunity, and hypersensitivity.'

9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis

A systematic review of economic evaluation studies of patients with lipodystrophy was included in the CS. Three economic evaluation studies were identified by the company. However, none of these studies were eligible for the economic evaluation of metreleptin, since the scope of all studies was not relevant to the CS.

A patient-level model was developed, aiming to assess the cost effectiveness of metreleptin versus standard of care for patients with lipodystrophy.

Individual patient data was obtained from the NIH follow-up study. A patient's survival probability is affected by abnormalities in a patient's heart, liver, kidney, or pancreas, i.e., the more organs with abnormalities, the higher the mortality for patients. Expected utilities and medical costs are based on the number of organ abnormalities. Each time point, health states are defined by the values of a set of attributes such as abnormalities of the liver, heart, kidney, and pancreas, retinopathy, neuropathy, amputation, impaired physical appearance, hyperphagia, and female reproductive dysfunction.

Health utility estimates were derived from a discrete choice experiment (DCE) within the general population. These estimates were used to estimate QALYs associated with lipodystrophy.

Metreleptin is available in 11.3 mg vials (10 mg dose). However, the availability of smaller vial sizes (5.8 mg and 3 mg) is expected within the next three months. Given the anticipated availability of smaller vials, an average per patient price of metreleptin was assumed in the base case analysis. Resource use was based on resource use questionnaires completed by two clinical advisers who treat lipodystrophy at Addenbrooke's Hospital. Health-state costs were based on NHS reference costs. Only the cost of hypoglycaemic events was included in the model as adverse event.

Several assumptions were assessed in the sensitivity analysis, i.e., a price fall of 90% of metreleptin after 10 years, reduced initial price, elimination of mortality benefit of metreleptin for PL patients, changes to assumptions regarding organ abnormality progression, alternate survival extrapolation methods, and earlier treatment initiation. A deterministic one-way sensitivity analysis was conducted for the key clinical and economic variables in the model. A probabilistic sensitivity analysis (PSA) was also conducted.

When only 11.3 mg vials were included in the cost effectiveness analysis, the incremental costs per QALY gained were £1,316,932 for metreleptin compared to SoC. The additional costs were £671,927 per QALY gained for metreleptin compared to SoC when multiple vial sizes of metreleptin are available. When a PAS was applied to the scenarios of only 11.3 mg vials available and multiple vial sizes available, ICER yielded [redacted] and [redacted] per QALY gained respectively for metreleptin versus SoC.

The ERG identified several critical issues with the company's economic analysis. One of the most important concerns related to the organ impairment progression, which led to bias in favour of metreleptin treatment compared to SoC. The ERG requested the company to conduct *de novo* statistical analyses. However, the company could not finalise this request given the timelines. The ERG also had serious concerns surrounding the survival analysis conducted by the company and the implementation of theses analyses in the model. There are also several issues identified by the ERG related to the extrapolation of other attributes not related to organ damage and metreleptin discontinuation, which created bias.

Furthermore, the ERG considers the disutility weights presented by the company as speculative. The key concern is that the use of DCE to directly obtain disutility values for heath states is still in its infancy. The most striking unresolved methodological issue relates to the fact that DCE classifies health states far more often below zero than TTO and produces lower average health state values. This was indeed observed in the results of the current DCE study. In addition, various major flaws in the design of the DCE and the analysis of the data were identified, leading to a negative assessment of the way QALYs are currently estimated.

The ERG also had several concerns about the resource use and costs included in the model. Furthermore, the ERG considered the validation of the model as insufficient.

Given the many critical issues described above, it proved impossible for the ERG to give any indication on the cost-effectiveness of metreleptin, and the uncertainty around the ICERs presented by the company goes far beyond that created by parameter uncertainty and reported in the CS.

The CS includes a budget impact model to estimate the total costs to the NHS for a period of five years of adopting metreleptin for LD patients in the UK. The budget impact analysis results presented by the company suggest that the net budget impact of implementing metreleptin will be £18,762,893 in year 1 and will rise to £34,114,350 in five years. The cumulative net budget impact over the first five years will be £133,045,965. Additionally, the estimated total number of LD patient eligible for metreleptin treatment after five years is 44 and the uptake of metreleptin rises from 85% in year 1 to 90% in year 5.

The CS also includes estimates of the impact of metreleptin on (i) inability to work or attend school for patients and carers; (ii) estimates of out-of-pocket costs for patients and carers including costs related to diabetes, transportation, fertility and cosmetic treatment; and (iii) other carer costs.

In general, the assumptions made in the budget impact analysis could be considered as plausible. However, there are some concerns about the expected uptake rate of metreleptin. The ERG considers the high expected uptake rate as reliable, but the reason behind the rising uptake rate from 85% in year 1 to 90% in year 5 is unclear since the company did not provide further details on these assumptions. Furthermore, the validity of the estimated discontinuation rate considered by the company remains unclear since detailed information on these assumptions were also not provided by the company.

The ERG has some concerns related to the impact of metreleptin beyond direct health benefits. No costs associated with inability to work or attending school were calculated in the analyses. However, as part of the NIH follow-up study, data on these attributes were collected. The ERG does not see that, while there were data collected on these attributes, it was not possible to estimate associated costs. The ERG also has a problem with the assertion in which the company stated that metreleptin will mitigate the costs of hospitalisation and fertility and cosmetic treatment, since this is not based on any evidence. No indirect health care costs, due to additional life-years after receiving metreleptin, were reported in the CS and the company expected that these costs would not influence the cost effectiveness results. In the opinion of the ERG, these costs should be included in the model for completeness. Finally, the CS does not include costs related to informal care and productivity loss for the caregiver. The company states that it is currently conducting research to gain more details of these issues, but the ERG considers it as inadequate that the impact of lipodystrophy on informal carers was not identified prior to the CS.

9.3 Strengths and limitations

9.3.1 Strengths of the CS

The ERG believes that the following represent strengths within the CS:

- The company's submission provided sufficient details for the ERG to appraise the searches, which were on the whole clear, transparent and reproducible. An adequate range of resources were searched.
- Despite the rarity of LD syndromes, the company has presented data from a large, multinational study of metreleptin treated patients.
- The ERG considers that the budget impact model is generally based on plausible assumptions.

9.3.2 Weaknesses of the CS

The following are the main weaknesses of the CS, observed by the ERG:

- The CS lacks information about the long-term effects of metreleptin treatment.
- The CS (section 9.9.2, page 121) states that: 'Over 85% of the 107 patients in study NIH 991265/20010769 received >1 year of metreleptin, 72% received >2 years, 54% received >3 years, and 28% received 6 or more years of metreleptin in this study. The maximum duration of therapy was 14 years.'[1] Despite this, the reporting of long-term clinical effectiveness outcomes, in the CS, was limited to information on the persistence (up to 36 months) of changes in HbA_{1c} and triglycerides on metreleptin treatment.
- Where long-term outcomes were available (in the NIH follow-up study, not included in the CS), these were either inferred from changes in surrogate outcome measures (e.g. hepatic enzymes, 24-hour protein excretion, blood pressure), or lacked any definition (e.g. hyperphagia recorded in notes).
- The CS lacks information about UK lipodystrophy patients; only one patient in the metreleptin treatment studies and one patient in the natural history study that was used in the cost effectiveness analysis, were UK patients.

- Despite the existence of an EAP, which includes UK patients and has been running for more than 10 years, no results from the EAP were included in the CS and no justification/explanation for this was provided.
- The study details and results for the NIH follow-up study and the GL/PL natural history study, which were used to inform cost effectiveness modelling, were not included in the clinical effectiveness section of the CS.
- Participants in the NIH follow-up study and the GL/PL natural history study were not comparable and it is not clear that the matching exercise reported in the CS was adequate to account for the apparent differences.
- The clinical effectiveness section of the CS does not include any assessment of the comparative effectiveness of metreleptin vs. standard care (either direct or indirect).
- The process used to identify and select comparator/natural history studies remains unclear; the company's response to clarification questions stated that: 'The clinical SLR was carried out to search for trials of both metreleptin and trials of relevant comparators (see Section 9.1 of the submission).'[39] However, the searches reported in the relevant sections of the CS were specific to metreleptin/leptin replacement interventions and did not include any terms to search for comparator studies; these searches would not have reliably retrieved studies of comparator interventions or natural history studies.
- There are several concerns related to the estimation of organ impairment progression. Due to these issues, the ERG has substantial concerns about the appropriateness of the statistical methods used by the company. Therefore, the ERG requested the company to conduct de novo statistical analysis, however, the company stated that they were not able to finalise this request due to the given timelines.
- Serious concerns regarding the survival analyses conducted by the company and the implementation of these analyses in the model were identified.
- There were also several issues related to the matching methodology conducted by the company.
- The ERG considers the derivation of the utility decrement from the company's DCE as invalid.
- The validation of the model is considered as inadequate and vague by the ERG.

9.4 Uncertainties

There is considerable uncertainty about the long-term effects of metreleptin treatment, particularly in relation to patient-perceived symptoms and clinical outcomes. The clinical effectiveness section of the CS includes only very limited evidence about patient perceived symptoms (hyperphagia) and clinical outcomes (liver damage) and data are limited to one year. The 'post-metreleptin improvements' reported in the NIH follow-up study,[46] but not in the CS, are frequently based on measures taken at one year and use definitions based on changes in surrogate outcome measures (e.g. improvement in liver abnormality is defined as 20% reduction in ALT/AST at year one in a patient who had elevated ALT/AST at baseline) or provide no definition at all. The NIH follow-up study[46] also included some information on newly emergent (on metreleptin treatment) lipodystrophy characteristics in patients with no evidence of these characteristics prior to metreleptin initiation. However, no indication of the timeframe

of observation was provided. Broadly, these data indicate that new incidences of organ abnormalities (liver, kidney and heart) and female reproductive dysfunction continue to occur, in all categories of LD patient, on metreleptin treatment. The data presented are insufficient to allow an adequate assessment of how the rate of development of new abnormalities on metreleptin treatment would compare with that seen in patients on standard care.

There remains some uncertainty regarding the long-term effects of metreleptin on metabolic measures. The CS includes some information on the persistence (up to 36 months) of changes in HbA_{1c} and triglycerides on metreleptin treatment (see Section 4.2.4). These data indicate that the apparent effect of metreleptin on triglyceride levels may not be applicable to the overall PL population. The potential effects of neutralising antibodies on the long-term efficacy of metreleptin treatment remain unclear. In clinical trials (studies NIH 991265/20010769 and FHA101), most patients (95%) developed antibodies to metreleptin.[33] Overall, in patients where antibody data was available, neutralising anti-drug antibody activity was observed in 38/102 patients (37%) and, of these 38 patients, 58% achieved resolution of neutralising antibodies.[33] Seven patients from the NIH and FHA101 studies developed high potency neutralizing activity to metreleptin.[75] One of these patients had loss of efficacy, as indicated by an increase in HbA_{1c} concentrations, and five hospitalisations due to bacterial infections.[75] A second patient, also with a history of hospitalisation for sepsis and worsening glycaemic control, was recently reported to have developed neutralising activity.[75] These cases raise concern that development of neutralising antibodies to metreleptin could impair metabolic control and immune function.[75]

The observed effects of metreleptin are all based on changes from baseline in single arm metreleptin treatment studies. The lack of comparative studies means that the extent to which any observed effects may be attributed to metreleptin remains unclear. This problem is compounded as the CS does not include any attempt to draw indirect comparisons through studies of the effects of established clinical management (diet, lifestyle modifications, lipid lowering drugs and anti-diabetic medications). The natural history study, used to provide comparator data for the cost effectiveness analysis, is not used in the clinical effectiveness sections of the CS and has a population which is not comparable to those included in the metreleptin intervention studies. It is therefore not possible to assess the extent to which any apparent treatment effects are attributable to metreleptin, or whether similar effects could be achieved using standard care.

The significance of pancreatitis, as an adverse event following withdrawal from treatment, remains unclear. The CS (section 9.7.2.5, pg 114) describes incidences of pancreatitis as an adverse event, following withdrawal from treatment: ‘Across the 148 patients included in LD studies, six (4%) patients (four with GL and two with PL), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and hypertriglyceridemia. One of the patients who developed septic shock concurrent with pancreatitis died; the other five patients recovered and continued on treatment. Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridemia and therefore increased risk of pancreatitis in the setting of

discontinuation of effective therapy for hypertriglyceridemia.'[1] Non-compliance rates of between 9% and 19% were reported,[1] and the extent of the pancreatitis risk, for these patients, remains unclear. The CS (section 9.9.1.1, page 120-121) states that: 'The identified risks of hypersensitivity, acute pancreatitis associated with metreleptin discontinuation, and hypoglycaemia with concomitant use of insulin and insulin secretagogues can be managed with risk communication in labelling and educational activities.'[1] However, no evidence is presented in support of this assertion. Similarly, the results for the NIH 991265/20010 study,[37] described in the CS, note the exclusion of an 'outlier' patient in whom an increase from baseline in triglycerides of >1000% at Month 12/LOCF was observed. This increase was attributed to non-compliance; the extent to which such large increases in triglycerides may be seen in patients who withdraw abruptly from metreleptin is unclear, and similarly the persistence and long-term consequences of any such increases is unknown.

There is no mention in the CS of possible stopping rules for metreleptin. The CS (Table A2, page 24-25) appears to assume that treatment will be ongoing for the full lifetime of the patient. However, given the many differences between and within groups of patients with different LD syndromes, it cannot be expected that the treatment works equally well or even at all in all patients and the effectiveness of the treatment might diminish over time. Therefore, stopping rules should be considered.

Currently, only 11.3 mg vials of metreleptin are available. However, the company expects the availability of smaller vial sizes (i.e., 5.8 mg and 3.0 mg) within three months after submission. This will impact the ICER significantly.

The ERG does not consider the cost-effectiveness model as reliable and trustworthy enough to inform decision making on the cost-effectiveness of metreleptin. The uncertainty around the company-reported ICERs is much larger than suggested by the PSA, which only addresses parameter uncertainty. However, the ERG still expects decision uncertainty to be rather low, as the ICER values, even in the best cases that the company presented, are significantly above the accepted thresholds.

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Appendix 1: ERG Search Strategies

ERG Epidemiology/Natural History Test Search

The following search was run to investigate additional condition terms identified by the ERG and to identify the number of records retrieved combining these with epidemiology/natural history terms. The ERG feels the number retrieved was a manageable number for the company to screen as part of their SLR to identify potential epidemiological and natural history studies.

Embase (OVIDSP): 1974 to 2018 March 07
Searched: 8.3.18

1 exp lipodystrophy/ (10776)
2 (lipodystrop$ or lipid dystroph$ or lipoatroph$ or FPLD or CGL2 or (Dunnigan adj syndrome$) or (lawrence adj syndrome$) or (Berardinelli$ adj syndrome$) or (wiedemann adj rautenstrauch) or (donohue adj syndrome$) or kobberling or koebberling).ti,ab,ot. (7234)
3 1 or 2 (13064)
4 incidence/ (299938)
5 standardized incidence ratio/ (2223)
6 Prevalence/ (570695)
7 standardized mortality ratio/ (2172)
8 demography/ (183246)
9 epidemiological data/ (29634)
10 mortality/ (689114)
11 disease progression/ (254412)
12 disease activity/ (69311)
13 morbidity/ (299793)
14 (occurrence$ or incidence$ or prevalence$ or episode$ or mortalit$ or morbidit$ or epidemiolog$ or demograph$ or (natural adj2 history) or (disease adj2 progres$) or (disease adj2 course)).ti,ab,ot. (3633979)
15 or/4-14 (4293380)
16 3 and 15 (2733)
17 limit 16 to yr="2008 -Current" (1540)

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Metreleptin for treating lipodystrophy (addendum)

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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The company has submitted updated cost-effectiveness analysis results based on the following new anticipated EMA license for metreleptin:

Metreleptin is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

1. with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above
2. with specialist-confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

This new label indication is different from the label indication used in the original company submission, namely the threshold age for metreleptin treatment for generalised LD patients is changed to 2 years old (6 years old in the original anticipated label indication) and all the blood-lab related threshold values for the partial LD patients in the original label indication are no longer used. From the NIH Follow-up study[1], 109 out of 112 patients would be eligible for the new indication (it was 80 out of 112 for the previously anticipated label indication).

In the first part of this addendum to the ERG report, the summary of the cost-effectiveness results based on the updated anticipated license will be provided and in the second part, corrections on the submitted model and the new results from the corrected addendum model will be explained.

Updated cost-effectiveness analysis results from the addendum submitted by the company

This section first summarises the headline results of the economic analyses presented by the company in its addendum. The company considered four different base case scenarios depending on the size of the vial and the price used for metreleptin. Thus, the results of the first base case scenario (BC1) are based on metreleptin list price and on a 10 mg vial size, which is currently being considered for marketing authorisation. However, it is expected that vials of 2.5 mg, 5 mg and 10 mg will be approved within three months after marketing authorisation. Therefore, the results of the second base case scenario (BC2) are based on metreleptin list price and all available vial sizes. The results of the third and fourth base case scenarios (BC3 and BC4) are obtained from BC1 and BC2 after applying a [redacted] Patient access scheme (PAS) price discount to metreleptin since the company expects this to be approved by the Patient access scheme liaison unit (PASLU). Table 1 summarises the results of the economic analyses conducted for the four base case scenarios described above. Note that only discounted results are presented and that the difference in scenarios is only on the costs side of the analysis.

Table 1: Summary economic analyses results – company base case scenarios (discounted)

	LYs	QALYs	Costs BC1	Costs BC2	Costs BC3	Costs BC4
Metreleptin	19.18	8.34	£11,199,165	£5,749,294	[redacted]	[redacted]
SoC	16.23	0.58	£74,854	£74,854	£74,854	£74,854
Incremental	2.95	7.77	£11,124,311	£5,674,440	[redacted]	[redacted]

ICER	--	--	£1,432,391/ QALY	£730,654/ QALY	[redacted]/ QALY	[redacted]/ QALY

Sources: Addendum submitted by the company reflecting updated anticipated label [2].

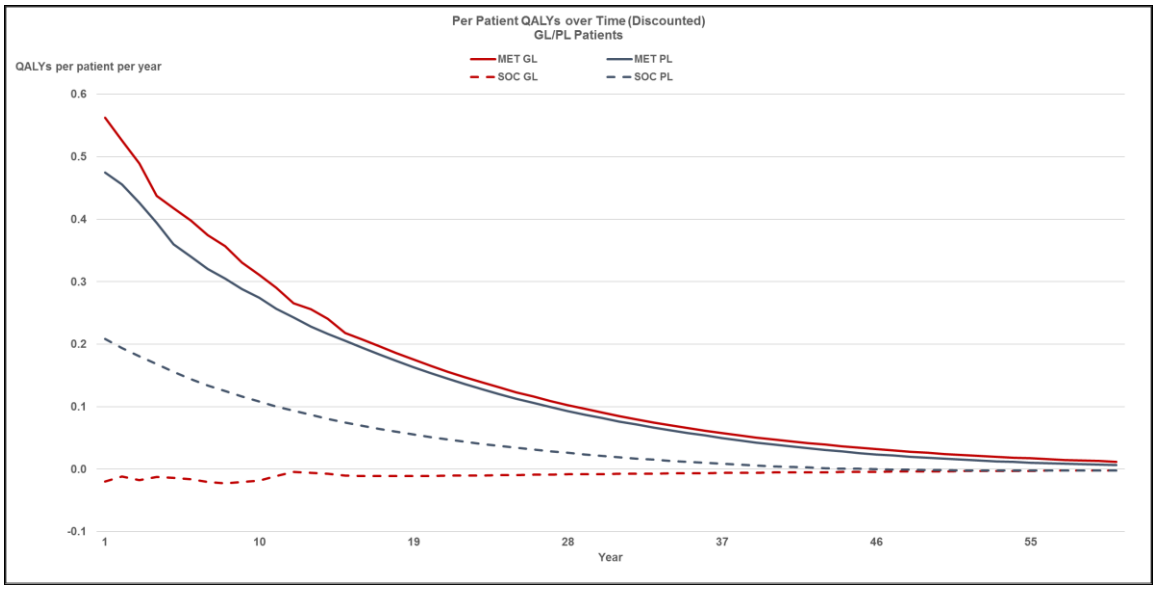
BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.

Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

In all base-case scenarios, more than 99% of the total costs for the metreleptin arm are due to the cost of the metreleptin therapy. Life years and quality adjusted life years (QALYs) are accrued over a time horizon of 90 years. On average, metreleptin resulted in 41.33 (undiscounted) life years and 16.27 QALYs, whereas the standard of care arm resulted in 33.07 life years but almost zero (0.27) QALYs. After discounting was applied, metreleptin resulted in 19.18 life years and 8.34 QALYs, and the standard of care arm resulted in 16.23 life years and 0.58 QALYs.

The distribution of the QALYs per patient per year for both treatment arms and partial lipodystrophy (PL) and general lipodystrophy (GL) patients separately is presented in Figure 1. In particular, this figure shows that for GL patients in the standard of care (SoC) arm the number of QALYs per year are always negative or zero suggesting that (from the general public point of view) these patients would rather die (at any time) than living with the disease.

Figure 1: QALYs per patient per year for metreleptin and SoC for PL and GL patients



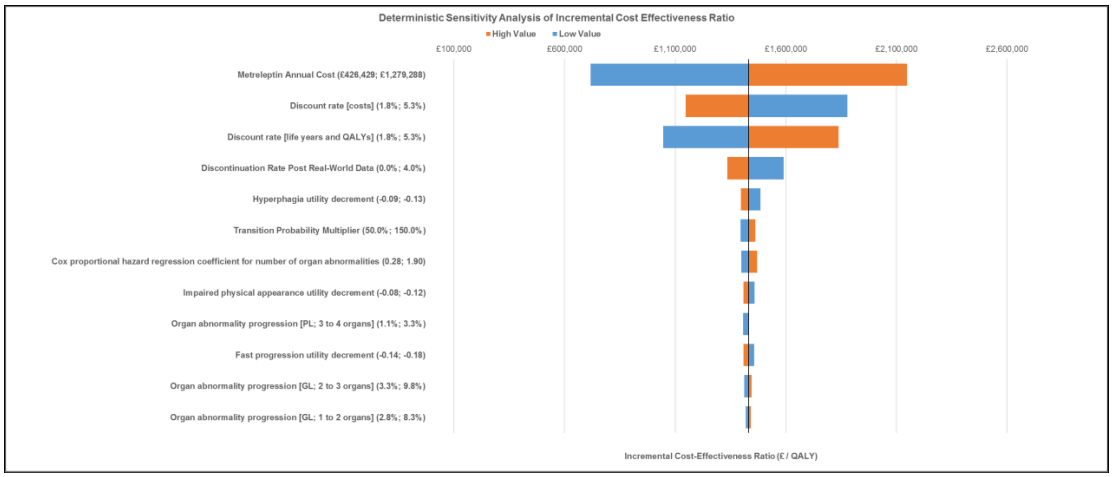
Source: Figure D26 in the addendum submitted by the company [2].

The company conducted a number of sensitivity and scenario analyses. The results of all these analyses are summarised below.

Sensitivity analyses included deterministic (DSA) and probabilistic sensitivity analyses (PSA). Univariate sensitivity analysis was performed on all single parameters of the model.

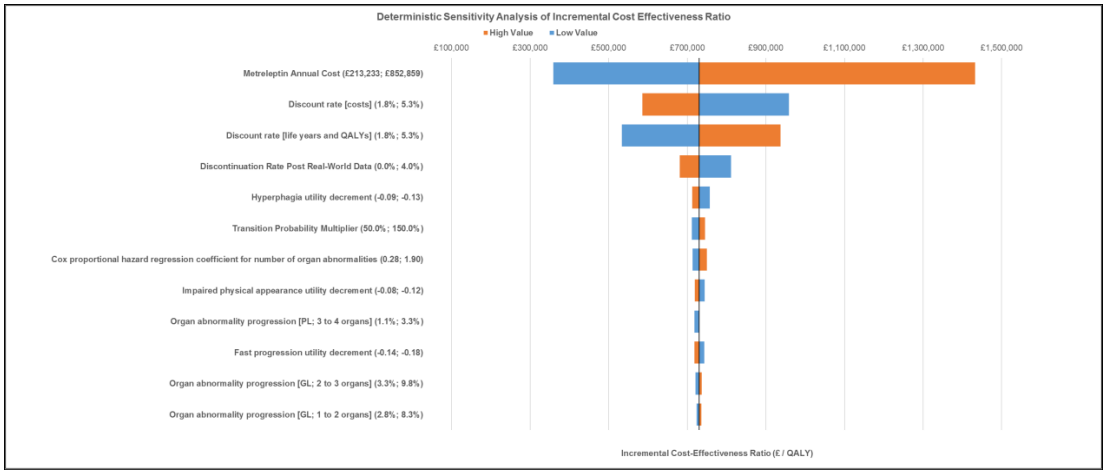
The results of the univariate DSAs were presented by the company as tornado diagrams and they are shown (for the four base case scenarios mentioned above) in the figures below. It was observed that in the four base case scenarios the metreleptin annual cost and the discount rates were the parameters for which the ICER was most sensitive. However, it should be noted that these parameters are typically not included in a DSA since they refer to structural/methodological uncertainty rather than parameter uncertainty. Besides these, the ICER was most sensitive to changes in the utility decrement due to hyperphagia and discontinuation rate.

Figure 2: Tornado diagram for BC1 – metreleptin list price and 10 mg vial size



Source: Figure D29 in the addendum provided by the company [2]

Figure 3: Tornado diagram for BC2 – metreleptin list price and multiple vial sizes



Source: Figure D30 in the addendum provided by the company [2]

Figure 4: Tornado diagram for BC3 – metreleptin PAS price and 10 mg vial size

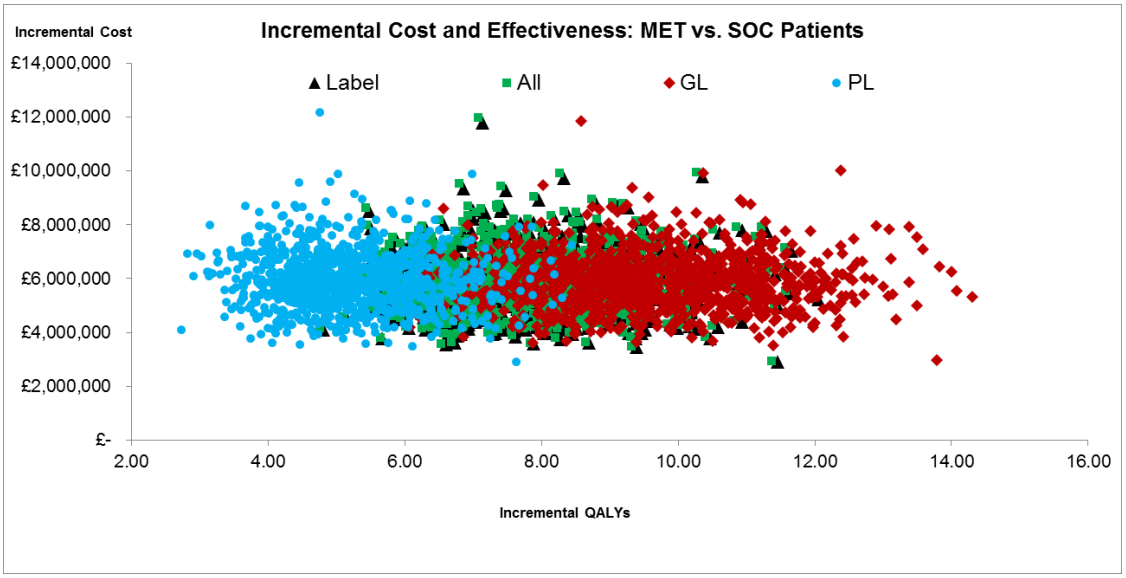
Source: Figure 1 in the updated PAS submission template in the addendum provided by the company [2]

Figure 5: Tornado diagram for BC4 – metreleptin PAS price and multiple vial sizes

Source: Figure 2 in the updated PAS submission template in the addendum provided by the company [2]

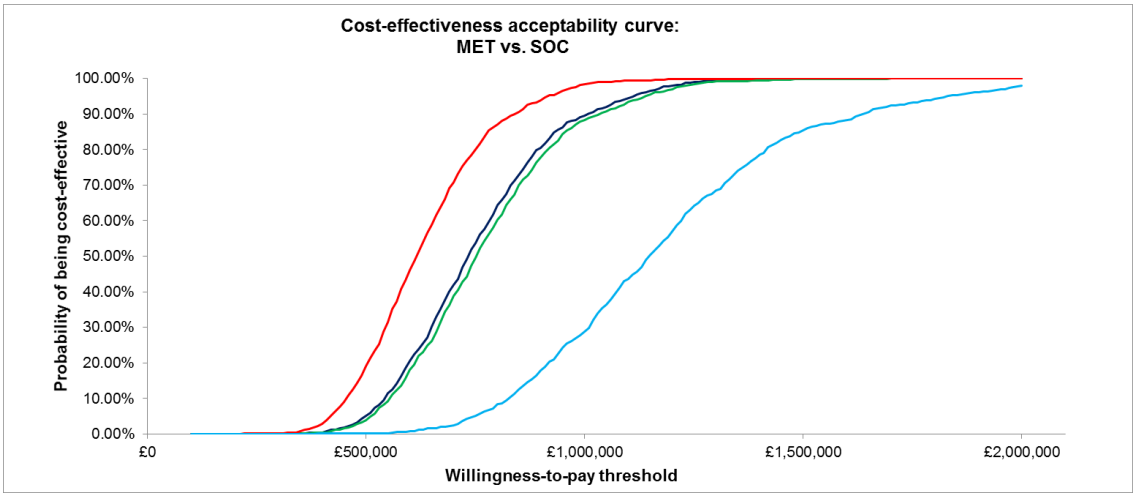
PSA was conducted using 1,000 model runs. The company presented results of the PSA as scatter plots of the total incremental costs and incremental QALYs on the CE plane and as cost effectiveness acceptability curves (CEACs). The PSA results were presented by the company for BC2 and BC4 only. The results of the two scenarios are presented in the figures below. Note that for BC1 and BC3, the only difference is on the cost side compared to BC2 and BC4. Therefore, the shape of the scatter plot of the PSA outcomes for BC2 and BC4 would be the same as that in BC2 and BC4, respectively, but shifted up on the incremental cost (Y) axis, which would result in less favourable CEACs for metreleptin.

Figure 6: PSA results on the CE plane – BC2: metreleptin list price and multiple vial sizes



Source: Figure 31 in the addendum provided by the company [2]

Figure 7: CEACs – BC2: metreleptin list price and multiple vial sizes



Source: Figure 32 in the addendum provided by the company [2]

Figure 8: PSA results on the CE plane – BC4: metreleptin PAS price and multiple vial sizes

Source: Figure 3 in the updated PAS submission template in the addendum provided by the company [2]

Figure 9: CEACs – BC4: metreleptin PAS price and multiple vial sizes

Source: Figure 4 in the updated PAS submission template in the addendum provided by the company [2]

The company conducted the scenario analyses on the updated cost-effectiveness model with the new anticipated licence. The results of this scenario analyses are shown in Table 2.

Table 2: Scenario analyses results

Scenario	Assumptions	QALYs gained	ICER BC1	ICER BC2	ICER BC3	ICER BC4
Base case	List price	7.77	£1,432,391	£730,654	--	--
Base case plus assume [redacted] lower price for metreleptin	List price with [redacted] discount	7.77	--	--	[redacted]	[redacted]
Base case plus alternate inputs	Doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension	9.30	£1,206,039	£615,167	--	--
Base case plus alternative inputs assume [redacted] lower price for metreleptin	List price with [redacted] discount, with multiple vial sizes, doubles hyperphagia disutility, incorporates heart abnormality improvement measured by hypertension	9.30	--	--	[redacted]	[redacted]
Future price changes: loss of metreleptin exclusivity	Metreleptin list price falls 90% after 10 years	7.77	£780,563	£398,469	[redacted]	[redacted]
Elimination of mortality benefit of metreleptin for PL patients	PL patient survival is predicted from the general population curve based on patient age, regardless of less of organ abnormality.	7.77	£1,438,784	£733,848	[redacted]	[redacted]
Changes to assumptions regarding organ abnormality progression: Slower or faster organ progression risk for both metreleptin and standard of care patients	all organ progression probabilities increased by 50%	7.54	£1,461,201	£745,356	[redacted]	[redacted]
	all organ progression probabilities decreased by 50%	8.05	£1,394,490	£711,266	[redacted]	[redacted]
Changes to assumptions regarding organ abnormality progression: Alternative standard of care progression rates	Unadjusted natural history study organ abnormality progression probabilities used for standard of care patients (See Table 1 in appendix 17.6.1)	8.02	£1,386,054	£707,002	[redacted]	[redacted]

Scenario	Assumptions	QALYs gained	ICER BC1	ICER BC2	ICER BC3	ICER BC4
Alternate survival extrapolation methods: GL curve parameterisation	Weibull	8.05	£1,409,130	£718,763	[redacted]	[redacted]
	Log Normal	7.93	£1,418,599	£723,623	[redacted]	[redacted]
	Logit	7.78	£1,430,755	£729,827	[redacted]	[redacted]
Alternate survival extrapolation methods: GL organ abnormalities	GL organ abnormality cox regression coefficient: [Lower DSA bound, 0.275]	7.84	£1,398,821	£713,389	[redacted]	[redacted]
	GL organ abnormality cox regression coefficient: [Upper DSA bound, 1.904]	7.59	£1,469,591	£749,796	[redacted]	[redacted]
Alternate survival extrapolation methods: PL organ abnormalities	Observed general population curve corresponds to an average of 1 abnormal organ (2.76 in base case)	7.48	£1,379,112	£703,720	[redacted]	[redacted]
Early treatment initiation at age 1 (CGL)	List price, multiple vial sizes	12.35	--	£865,667	--	[redacted]
Early treatment initiation at age 1 (CGL) plus alternate inputs	List price, multiple vial sizes plus double hyperphagia decrement, plus parental disutility of -0.05 per period	14.51	--	£736,750	--	[redacted]

Sources: Table D51, D52,53 in the addendum and Table 5, 6,7 in the updated PAS submission template in addendum [2].
BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.
Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

ERG Comment:
Similar to the original submission, one of the lowest ICER ([redacted]) was found for the scenario with [redacted] discount on metreleptin list price, assuming multiple vial sizes, doubled hyperphagia disutility and incorporating heart abnormality improvement measured by hypertension. The company argued that this scenario reflected the true metreleptin benefit. However, the ERG does not agree with that statement because there is no evidence that hyperphagia disutility should be twice as high from its DCE study estimate and also the argument that hypertension improvement is a surrogate for heart organ abnormality is deemed to be not convincing by the ERG.

The ERG could not replicate the last two scenario results, where the impact of early initiation of metreleptin treatment for CGL patients was explored (from age 1). The company did not provide any details on these scenarios; hence the ERG cannot comment on the plausibility of the assumptions taken while conducting these early treatment initiation scenario analyses.

Similar to the company submission and clarification letter response models, the addendum CE model is also based on non-reliable evidence and unjustified assumptions. More specifically, the RWD data used to estimate important inputs for the model is not reliable (e.g. twice data updates without being able to track what was been updated and how, vague definitions of organ impairment were applied). Additionally, both the methods used in quantifying the treatment effect and the DCE methodology used were not transparently reported but more importantly not credible.

The next chapter outlines the additional analyses conducted by the ERG, with the aim of addressing some of the problems identified in the critical appraisal of the economic analysis.

ERG exploratory analyses on the addendum model
The ERG realised that there were additional changes in the addendum model, other than the updated label indication. These changes were not reported and led to differences in model results. The ERG identified these unreported changes as below:

1. The addendum model[2] used slightly different proportional hazard regression coefficients compared to the models used in the CS [3]. The differences can be seen in Table 3.

Table 3: Hazard regression coefficients used in the addendum and company submission models

	Addendum model	Model in the company submission
Cox proportional hazard regression coefficient (GL)	1.09	1.089700
Average Organ Abnormality Level (PL)	2.76	2.757353
Average Organ Abnormality Level (GL)	2.76	2.757353
Cox proportional hazard regression coefficient (PL)	1.53	1.531200

2. The hypoglycemic event that occurred in the 11th year of the 12th patient was deleted.

3. Irrelevant calculations in the organ impairment real world data sheets were mistakenly taken into consideration in the cells corresponding to the 63rd and 64th year calculations in the organ impairment simulation sheets.
4. The missing baseline leptin levels are replaced with 9999, so that these patients will be always considered to fall under the updated license indication.

Except for the last one, the ERG undid these changes in the addendum model, so that the addendum and the previous company submission models are the same except for the updated label indication. The ERG also identified the following errors in the company model:

- Wrong transition probability is used for the fourth organ impairment annual probability for SoC
- The costs and disutilities associated with organ impairments were wrongly calculated, and different formulae were used for SoC and metreleptin arms

The addendum model's results after correcting these errors can be seen in Table 4 below.

Table 4: Summary economic analyses results – corrected company base case scenarios (discounted)

	LYs	QALYs	Costs BC1	Costs BC2	Costs BC3	Costs BC4
Metreleptin	19.26	9.33	£11,202,756	£5,751,126	[redacted]	[redacted]
SoC	16.44	1.60	£72,635	£72,635	£72,635	£72,635
Incremental	2.82	7.73	£11,130,121	£5,678,491	[redacted]	[redacted]
ICER	--	--	£1,440,738/ QALY	£735,052/ QALY	[redacted] QALY	[redacted] QALY

BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.

Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, LYs = life-years, QALYs = quality-adjusted life years, SoC = standard of care

As observed in Table 4, these errors do not seem to have a major effect on the addendum company base-case cost-effectiveness results (comparing to the values in Table 1). The ICERs in all base-case scenarios have slightly increased.

Since the addendum model changes are only related with the label indication population, the subgroup analysis results (focusing on subgroups that are not based on indication label) in the corrected addendum model are the same as the ones in the corrected CS model.

Additional scenario analyses conducted on the corrected base-case model

The ERG conducted six additional scenario analyses to explore structural and input parameter uncertainty. These scenarios are described below:

- Scenario 1: The impact of metreleptin discontinuation was reflected in not only in organ impairment progression, but also in the progression of other disease attributes. For instance, when a patient on metreleptin discontinues the treatment, the corresponding

values from the SoC arm were assumed for discontinued patients' blood-lab and other attributes (e.g. hyperphagia, ability to work, etc.)

- Scenario 2: Abandoning the logical constraint imposed on the SoC arm patients, which never allowed them to have fewer number of organ impairments than metreleptin
- Scenario 3: Assuming that there is no difference between the SoC and metreleptin treatments in terms of the disease attributes other than organ impairment and blood-lab values (e.g. hyperphagia, ability to work, physical appearance, etc.) during a patient's lifetime
- Scenario 4: Using utility input from Dhankar et al. (0.67) for all the years that a patient is alive
- Scenario 5: Except for the data at baseline, no real-world data is directly used in the simulation of the organ/blood-lab attributes for the metreleptin arm patients
- Scenario 6: For the disutility and cost calculations associated with the number of organs impaired, the corrected formula from the metreleptin arm (assuming independent application of the organ specific abnormality probability weights) is used in both arms.

Results of the ERG's exploratory scenario analyses

The results from these exploratory scenario analyses are given in Table 5 below.

Table 5: Exploratory scenario analyses from the ERG

Scenario	Assumptions	QALYs metreleptin	QALYs SoC	QALYs gained	ICER BC1	ICER BC2	ICER BC3	ICER BC4
Base case		9.33	1.6	7.73	£1,440,738	£735,052	[redacted]	[redacted]
Scenario 1	The impact of metreleptin discontinuation in other attributes	7.29	1.60	5.69	£1,955,739	£997,801	[redacted]	[redacted]
Scenario 2	Abandoning the logical constraint imposed on the SoC arm patients	9.33	1.62	7.71	£1,443,359	£736,388	[redacted]	[redacted]
Scenario 3	No change between the SoC and metreleptin treatments in terms of attributes other than organ impairment and blood-lab values	3.56	1.60	1.96	£5,683,204	£2,899,521	[redacted]	[redacted]
Scenario 4	Using utility input from Dhankar et al. for all the alive years of the patient	12.90	11.02	1.89	£5,898,649	£3,009,439	[redacted]	[redacted]
Scenario 5	Except for the data at baseline, no real-world data is directly used in the simulation of the organ/blood-lab attributes for the metreleptin arm patients	7.26	1.63	5.64	£1,859,171	£948,041	[redacted]	[redacted]
Scenario 6	Alternative organ impairment associated cost/disutility calculation	8.45	0.64	7.81	£1,425,279	£726,954	[redacted]	[redacted]

BC1: metreleptin list price and 10 mg vial size, BC2: metreleptin list price and multiple vial size, BC3: metreleptin PAS price and 10 mg vial size, BC4: metreleptin PAS price and multiple vial size.
Abbreviations: BC = base case, ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care

As with the analyses in the ERG report, in this addendum, scenarios 3 and 4 had the highest impact on the results since the ICERs in these scenarios are three-fold larger than the ICER from the base case(s).

In scenario 3, the treatment effect of metreleptin on attributes like hyperphagia, ability to work was assumed to be zero. The impact on the ICER suggests that the treatment effect of metreleptin on these attributes is one of the key drivers of the cost effectiveness. It should be noted that the evidence on the effectiveness of metreleptin for these attributes was weak, future research is highly likely to reduce this uncertainty.

Since the ERG was concerned about the utility estimates provided by the company (including the overall methodological DCE approach), scenario analysis 4 demonstrated how different the utility estimates used in the submission were compared to the EQ5D values from the literature and how changing the utility input to the model can change the results substantially

Discussion

As discussed in the ERG report, the ERG considers that the evidence base used in this cost effectiveness analysis is not reliable and trustworthy enough to inform decisions on metreleptin. However, the ERG expects that the decision uncertainty from the payer perspective related to metreleptin's value for money would be rather low, in view of the fact that the ICER estimates from all analyses, including the analyses with PAS discounts, are markedly above the acceptable thresholds considered for orphan drugs.

References

[1] Aegerion Pharmaceuticals Ltd. *Metreleptin for treating lipodystrophy [ID861]: response to request for clarification from the ERG*: Aegerion Pharmaceuticals Ltd., 2018. 98p.

[2] Aegerion Pharmaceuticals Ltd. *Metreleptin for treating lipodystrophy [ID861]: addendum to submission to National Institute of Health and Care Excellence. Highly Specialised Technologies Programme (HST)*: Aegerion Pharmaceuticals Ltd., 2018. 20p.

[3] Aegerion Pharmaceuticals Ltd. *Metreleptin for treating lipodystrophy [ID861]: submission to National Institute of Health and Care Excellence. Highly Specialised Technologies Programme (HST)*: Aegerion Pharmaceuticals Ltd., 2018. 280p.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Metreleptin for treating lipodystrophy [ID861]

You are asked to check the ERG report from Kleijnen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Friday 18 May 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Summary: Numerical data error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 12 of the ERG report where it states: In study FHA101, mean actual change from baseline to Month	Please change to: In study FHA101, mean actual change from baseline to Month 12/LOCF for HbA1c was -1.2% (95% CI: -4.3 to 2.0) for GL patients and -	The ERG have reported the results for study NIH 991265/20010769; please amend to the correct values as shown (from Table 24 in the	The company is correct. Correction made.

12/LOCF for HbA1c was -1.2% (95% CI: -4.3 to 2.0) for GL patients and **-0.9% (95% CI: 95% CI: -1.4 to 0.4)** for patients in the PL subgroup.	**0.8% (95% CI: -2.5 to 0.9)** for patients in the PL subgroup.	company submission [CS] and Table 12 in the CSR). Please also delete the extra "95% CI"	

Issue 2 Non-compliance rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 of the ERG report where it states: With reported non-compliance rates of between **9%** and 19% the extent of the pancreatitis risk, for these patients, remains unclear and would appear to warrant further consideration. Pg 99 of the ERG report where it states: Non-compliance rates of between **9%** and 19% were reported,[1] and the extent of the pancreatitis risk, for these patients, remains unclear. Pg 183 of the ERG report where it states: Non-compliance rates of between **9%** and 19% were reported,[1] and the extent of the pancreatitis risk, for these patients, remains unclear.	On page 17 please change to: With reported non-compliance rates of between **8%** and 19%,[1] the extent of the pancreatitis risk for these patients remains unclear and would appear to warrant further consideration. On page 99 please change to: Non-compliance rates of between **8%** and 19% were reported,[1] and the extent of the pancreatitis risk, for these patients, remains unclear. On page 183 please change to: Non-compliance rates of between **8%** and 19% were reported,[1] and the extent of the pancreatitis risk, for these patients, remains unclear.	The value of 9% is incorrect and should be 8% (Table C18 in CS and Table 8 in CSR).	The company is correct, the lower estimate of non-compliance rates should have been reported as 8%. However, we do not believe that this difference effects the issue described and hence it does not require an addendum.

Issue 3 Population: Numerical data error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 of the ERG report where it states: Five of the 66 GL patients included in the NIH 991265/20010769 were under six years of age and one was under two years of age, 40/66 (60.6%) of GL patients and 16/31 (51.6%) of PL subgroup patients had triglyceride levels <5.65 mmol/L, and **17/66 (25.8%)** of GL patients and 2/31 (6.5%) of PL subgroup patients had HbA_{1c} <6.5%.	Please change to: Five of the 66 GL patients included in the NIH 991265/20010769 were under six years of age and one was under two years of age, 40/66 (60.6%) of GL patients and 16/31 (51.6%) of PL subgroup patients had triglyceride levels <5.65 mmol/L, and **15/66 (22.7%)** of GL patients and 2/31 (6.5%) of PL subgroup patients had HbA_{1c} <6.5%.	The value of 17/66 (25.8%) is incorrect (see NIH 991265/20010769 CSR Table 13)	The company is correct. Correction made.

Issue 4 Population: text error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 of the ERG report where it states: None of the patients in the FH101 study were under six years of age, however, 6/9 (66.7%) of GL patients and 6/7 (85.7%) of PL patients had triglyceride levels <5.65 mmol/L, and 3/9 (33.3%) of GL patients and 1/7 (14.3%) of **PL patients** had HbA1c <6.5%	Please change to: None of the patients in the FH101 study were under six years of age, however, 6/9 (66.7%) of GL patients and 6/7 (85.7%) of PL patients had triglyceride levels <5.65 mmol/L, and 3/9 (33.3%) of GL patients and 1/7 (14.3%) of **PL subgroup patients** had HbA1c <6.5%	The reported value corresponds to the PL subgroup patients and not PL patients overall (see study FH101 CSR Table 11)	The company is correct. Correction made.

Issue 5 Persistence of change in HbA1c and triglycerides over time: typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 of the ERG report where it states: The LS mean (SEM) percentage change values were as follows: month 12 = -16.7 (8.62), p = 0.054; month 24 = -9.4 (16.41), p = 0.566; month 36 =4.4 (17.53), **p = 0/801**; overall MMRM = -8.3 (5.46), p=0.131.	Please change to: The LS mean (SEM) percentage change values were as follows: month 12 = -16.7 (8.62), p = 0.054; month 24 = -9.4 (16.41), p = 0.566; month 36 =4.4 (17.53), **p = 0.801**; overall MMRM = -8.3 (5.46), p=0.131.	This was a typo	The company is correct. Correction made.

Issue 6 Subgroup data for genetic and acquired LD syndromes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 34 of the ERG report where it states: The clinical effectiveness section of the CS did not include any subgroup data for genetic and acquired LD syndromes.	Please delete the sentence: The clinical effectiveness section of the CS did not include any subgroup data for genetic and acquired LD syndromes.	Subgroup data for genetic (Congenital/ Familial) and acquired LD syndromes is presented in Table C23 of the CS.	The company is correct. We apologise that these data were overlooked and have deleted the sentence.

Issue 7 Supporting reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 43 of the ERG report where it states: The two publications, relating to one systematic review and listed in Table 3, were mentioned in the CS (section 9.2.2, page 69), but no references were provided; copies of the	Please change to: The two publications, relating to one systematic review and listed in Table 3, were mentioned in the CS (section 9.2.2, page 69), but no references were provided; copies of the articles **were not provided in the CS but were provided in the response to clarification**	The copies of the articles (Rodriguez, and Paz-Filho 2014) were provided with the response to clarification questions on 27th February	Not a factual error, copies of the articles were not provided.

articles **were not provided in either the CS or the response to clarification questions**.	**questions**.		

Issue 8 Data from the NIH follow-up study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80 of the ERG report where it states: However, it should be noted that heart abnormalities included hypertrophy, any dilation, any regurgitation, cardiomyopathy, and tachycardia and only **27/50 (54%)** of patients with a pre-treatment heart abnormality were also classified as hypertensive or pre-hypertensive;	Please change to: However, it should be noted that heart abnormalities included hypertrophy, any dilation, any regurgitation, cardiomyopathy, and tachycardia and only **29/50 (58%)** of patients with a pre-treatment heart abnormality were also classified as hypertensive or pre-hypertensive;	The ERG have used a draft version of the NIH follow-up study report provided on February 27 rather than the final version provided on March 2. The values from the final version are now provided in cases where they were different. There were also some additional errors which have been corrected.	Not a factual error. The ERG received only one 'study report' document in relation to the NIH follow-up study; this document was received in response to the request for clarification. Additional spreadsheets were provided in support of the additional analyses requested, but we are not able to check these (within the time available) for variations from the 'study report' provided.
Page 80 of the ERG report where it states: Based on these criteria, **19/46 (41%)** of GL patients and **4/25 (16%)** PL patients were classified as having experienced an improvement in their kidney abnormality over one year of metreleptin treatment. However, it	Please change to: Based on these criteria, **16/46 (35%)** of GL patients and **3/25 (12%)** PL patients were classified as having experienced an improvement in their kidney abnormality over one year of metreleptin treatment. However, it should be noted that kidney abnormalities included proteinuria, enlarged kidneys, nephropathy,		See above

should be noted that kidney abnormalities included proteinuria, enlarged kidneys, nephropathy, hydronephrosis, renal disease, nephromegaly, renal failure, renal calculus, and glomerulosclerosis and only **38/74 (51%)** of patients with a pre-treatment kidney abnormality also had elevated 24 hour protein excretion; one year changes in 24 hour protein excretion alone are unlikely to provide an adequate indicator of long term clinical improvement/progression for the conditions listed. Of the 22 GL patients who had no evidence of kidney abnormalities before metreleptin treatment, **eight (36%)** had emergent kidney abnormalities after metreleptin initiation, and **4/19 (21%)** of PL patients who had no evidence of heart abnormalities before treatment had emergent abnormalities after metreleptin initiation.[2] No indication of mean/median length of follow-up was provided.	hydronephrosis, renal disease, nephromegaly, renal failure, renal calculus, and glomerulosclerosis and only **38/71 (54%)** of patients with a pre-treatment kidney abnormality also had elevated 24 hour protein excretion; one year changes in 24 hour protein excretion alone are unlikely to provide an adequate indicator of long term clinical improvement/progression for the conditions listed. Of the 22 GL patients who had no evidence of kidney abnormalities before metreleptin treatment, **11 (50%)** had emergent kidney abnormalities after metreleptin initiation, and **9/19 (47%)** of PL patients who had no evidence of heart abnormalities before treatment had emergent abnormalities after metreleptin initiation.[2] No indication of mean/median length of follow-up was provided.		
Page 82 of the ERG report where it states: With respect to lipid-lowering medication, 19/35 (54.3% of GL	Please change to: With respect to lipid-lowering medication, 19/35 (54.3%**)** of GL patients and 16/38 (**42.1%**) of PL patients were able to discontinue lipid lowering		Correction made.

patients and 16/38 (68.2%) of PL patients were able to discontinue lipid lowering medications.[2]	medications.[2]		

Issue 9 Data from the GL/PL natural history study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83 of the ERG report where it states: Over the whole observation period, **2/15 (13.3%)** of female GL patients and **15/41 (36.6%)** of female PL patients were found to have reproductive dysfunction.[3]	Please change to: Over the whole observation period, **11/33 (33.3%)** of female GL patients and **34/85 (39.5%)** of female PL patients were found to have reproductive dysfunction.[3]	The reported values are the baseline values rather than over the whole observation period	The company is correct. Correction made.

Issue 10 HIV-associated LD

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 of the ERG report where it states: An important sub-type of acquired LD occurs with prolonged exposure to protease-inhibitor-containing antiretroviral therapy in HIV-infected patients.[4] **ERG comment:** The CS reports the exclusion of specific aetiologies of acquired LD (table C11, page 69 of the CS): • HIV-associated LD • LD secondary to drug administration (insulin	On page 21 please change to: An important sub-type of acquired LD occurs with prolonged exposure to protease-inhibitor-containing antiretroviral therapy in HIV-infected patients.[4] **ERG comment:** The CS reports the exclusion of specific aetiologies of acquired LD (table C11, page 69 of the CS): • HIV-associated LD • LD secondary to drug administration (insulin growth hormone, steroids, antibiotics and vaccinations) • LD secondary to systemic diseases such as uncontrolled diabetes	The indication for metreleptin will not include HIV-associated LD (please see pg 19 of the Response to consultee and commentator comments on the draft remit and draft scope (pre-referral available from https://www.nice.org.uk/guidance/gid-hst10011/documents/scope-consultation-comments-and-responses) and QA5 in the response to clarification questions, where we stated "HIV-associated LD was considered an exclusion criteria because metreleptin is not indicated in this population."	Not a factual error

growth hormone, steroids, antibiotics and vaccinations) • LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections The scope issued by NICE does not **exclude** these sub-types of LD. Furthermore, the search strategies reported in the CS, for both clinical evidence (Appendix 1, page 220-223 of the CS) and economic evidence (Appendix 3, page 225-227 of the CS) included terms for HIV-associated LD. Page 39 of the ERG report where it states: In addition, a number of exclusion criteria are listed for population (HIV-associated LD, LD secondary to drug administration, LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and	mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections The scope issued by NICE does not specify whether these sub-types of LD are included, however the exclusion is in-line with the final expected metreleptin license. On page 39 please change to: In addition, a number of exclusion criteria are listed for population (HIV-associated LD, LD secondary to drug administration, LD secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections), which is in-line with line with the final expected metreleptin license.	Metreleptin is a leptin replacement therapy administered to address the effects of leptin deficiency in the population of LD patients with low leptin levels (CS Section 2.2). It is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency (CS Section 3.1). Because there is no evidence that leptin deficiency is a cause of HIV-LD and the other types e.g LD secondary to drug administration and LD secondary to systemic diseases),[4] these types are not considered under the marketing authorisation for metreleptin. The US prescribing information states that: MYALEPT is not indicated for use in patients with HIV-related lipodystrophy or for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridaemia, without concurrent evidence of congenital or acquired generalised lipodystrophy.[5] The final NICE scope describes the 4 main categories of LD in the background section: GCL, AGL, FPL and APL. This is in-line with the proposed marketing authorisation (CS Section 3.1). The publication by Garg et al 2011 cited	

chronic infections), which are not consistent with either the NICE scope.		by the ERG in their report describes HIV-associated LD and localized lipodystrophy (e.g drug-induced) as separate categories to the above 4.[4] Nowhere in the CS or the final scope is there any mention of the subtype of HIV-associated LD as a relevant population to be considered; for example, it is not in any of the background information, it was an exclusion criteria in the clinical trials and also in the clinical SLR. Data from clinical trials do not support the safety and efficacy in patients with HIV-related LD (see draft SmPC submitted with the CS).[6]	

Issue 11 Estimates of the numbers of UK patients eligible for metreleptin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 of the ERG report where it states: The CS estimates of the numbers of UK patients eligible for metreleptin treatment appear low when compared to published estimates of the prevalence of LD [Chiquette paper]; the number of patients currently treated divided by the estimated total population for England and Wales 26/58.38 million gives an estimated	The CS estimates of the numbers of UK patients eligible for metreleptin treatment appear low when compared to published estimates of the prevalence of LD [Chiquette paper]; the number of patients currently treated divided by the estimated total population for England and Wales 26/58.38 million gives an estimated prevalence of approximately 0.45 cases/million. **The company provided reasons for this in the clarification questions.**	Factually, the company gave a detailed reason for this in the clarification questions (see Question A16); however, none of the reasons have been incorporated into the ERG report. As a matter of factual accuracy, we think the ERG should recognise this at least.	Not a factual error. The company provided a critique of the Chiquette paper, however, this does not alter the substantive point, which is that there is uncertainty around this issue.

prevalence of approximately 0.45 cases/million. **The reason for this discrepancy is unclear.**			

Issue 12 Study about hypertriglyceridemia and heart disease in LD

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22 of the ERG report where it states: The CS tends to overstate the evidence about hypertriglyceridemia and heart disease in LD. For example, section 6.1.3.1, pages 37-38 of the CS, states: 'In the Copenhagen City Heart Study, which was initiated in 1976 and has followed 19,329 subjects, each 1 mmol/L increase in triglycerides is associated with a 40% increase in risk for myocardial infarction (MI), a 25% increase in risk for ischemic heart disease, and an 18% increase in risk of death in women, and 16%, 12%, and 10% increased risks, respectively, in men, **when adjusted for age and HDL-C.**'[1] **These numbers are not reported in the cited study and are not consistent with the multifactorially adjusted hazard**	Please change to: The CS tends to overstate the evidence about hypertriglyceridemia and heart disease in LD. For example, section 6.1.3.1, pages 37-38 of the CS, states: 'In the Copenhagen City Heart Study, which was initiated in 1976 and has followed 19,329 subjects, each 1 mmol/L increase in triglycerides is associated with a 40% increase in risk for myocardial infarction (MI), a 25% increase in risk for ischemic heart disease, and an 18% increase in risk of death in women, and 16%, 12%, and 10% increased risks, respectively, in men, when adjusted for age and HDL-C.'[1] These numbers are not reported in the cited study **but are consistent with hazard ratios (HRs) adjusted for age and HDL-C. However the** multifactorially adjusted hazard ratios (HRs) are: For women these were 1.20 (95% CI: 1.05 to 1.37) for MI, 1.10 (95% CI: 0.99 to 1.21) for ischaemic heart disease and 1.18 (95% CI: 1.10 to 1.27) for total death; for men the corresponding values were 1.04 (95% CI: 0.98 to 1.11) for MI, 1.00 (95% CI: 0.95 to 1.06) for ischaemic heart disease and 1.08 (95%	In the cited study the age and HDL-C adjusted HRs are: For women these were 1.41 (1.26-1.57); for MI, 1.25 (1.14-1.37); for ischaemic heart disease and 1.18 (1.11-1.26) for total death For men the corresponding values were 1.16 (95% CI 1.10 to 1.22) for MI, 1.12 (95% CI: 1.07 to 1.18) for ischaemic heart disease and 1.10 (95% CI: 1.06 to 1.15). Therefore, the statement in the CS is consistent with the age and HDL-C adjusted HRs cited in the Copenhagen City Heart Study (please see Table 2, page 306 in Nordestgaard 2007) [8].	Not a factual error

ratios (HRs) which are reported: For women these were 1.20 (95% CI: 1.05 to 1.37) for MI, 1.10 (95% CI: 0.99 to 1.21) for ischaemic heart disease and 1.18 (95% CI: 1.10 to 1.27) for total death; for men the corresponding values were 1.04 (95% CI: 0.98 to 1.11) for MI, 1.00 (95% CI: 0.95 to 1.06) for ischaemic heart disease and 1.08 (95% CI: 1.03 to 1.13).[8]	CI: 1.03 to 1.13). [8]		

Issue 13 Risk of pancreatitis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93 of the ERG report where it states: Across the 148 patients included in LD studies, six (4%) patients (four with GL and two with PL), experienced treatment emergent pancreatitis.[6,9,10] All patients had a history of pancreatitis and hypertriglyceridemia.[6,9,10] One of the patients who developed septic shock concurrent with pancreatitis died; the other five patients recovered and continued on treatment.[6,9,10] Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence	Please delete the following: Tables C18 and C19 (pages 86-87 of the CS) describe the number of premature discontinuations in study NIH 991265/20010769 and study FHA101 respectively.[1] In Table C18 23/66 (34.8%) GL patients; 15/41 (36.6%) PL patients and 11/31 (35.5%) PL subgroup patients prematurely discontinued. In Table C19 4/9 (44.4%) GL patients; 20/32 (62.5%) PL patients and 2/7 (28.6%) PL subgroup patients prematurely discontinued. The numbers of patients who discontinue treatment are alarmingly high given that discontinuation of treatment appears to be associated with an increased risk of pancreatitis.	The reasons for discontinuation in Table C18 for study NIH 991265/20010769 included noncompliance; death; ineligibility determined; adverse event; lost-to-follow up; transferred to other program; lack of efficacy/no benefit. In Table C19 for study FHA101 the reasons for discontinuation included adverse event, lost-to follow up, death, physician decision, withdrawal by patient. There were no discontinuations due to non-compliance. The values quoted do not equate to abrupt interruption and/or non-	Not a factual error

of pancreatitis in several of these patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridemia.[6] **ERG comment:** The CS describes abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. Tables C18 and C19 (pages 86-87 of the CS) describe the number of premature discontinuations in study NIH 991265/20010769 and study FHA101 respectively.[1] In Table C18 23/66 (34.8%) GL patients; 15/41 (36.6%) PL patients and 11/31 (35.5%) PL subgroup patients prematurely discontinued. In Table C19 4/9 (44.4%) GL patients; 20/32 (62.5%) PL patients and 2/7 (28.6%) PL subgroup patients prematurely discontinued. The numbers of patients who discontinue treatment are alarmingly high given that discontinuation of treatment appears to be associated with an increased		compliance, as has been implicated by the ERG in the context of this paragraph. Please also note that all patients who experienced treatment emergent pancreatitis had a history of pancreatitis and hypertriglyceridemia. In addition, the identified risks of acute pancreatitis associated with metreleptin discontinuation can be managed with risk communication in labelling and educational activities,[6,9,10] (see CS section 9.2.2.7). The draft SmPC submitted with the CS states:[6] Non-compliance with or abrupt discontinuation of Myalepta may result in worsening hypertriglyceridaemia and associated pancreatitis, particularly in patients with risk factors for pancreatitis (e.g. history of pancreatitis, severe hypertriglyceridaemia). Tapering of the dose over a two-week period is recommended in conjunction with a low fat diet. The paragraph to be deleted does not reflect any of this evidence, hence we believe to be factually inaccurate.	

risk of pancreatitis.			

Issue 14 Reporting of clinical results and comparator data in the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83 of the ERG report where it states: The CS did not report any comparator results for development and progression of liver disease (from the GL/PL natural history study)	Please delete the statements as reported in the "description of problem" column and for the columns below	Although these data were not in the clinical-effectiveness section, they were reported in the cost-effectiveness of the CS. In addition, all the detailed clinical data were provided in response to clarification questions by 2nd March, which the ERG has not mentioned in several instances where they talk of a lack clinical data. Please correct/clarify this throughout the report, as to be more factually accurate the report should refer to the information being received in the clarification questions response. Please see the below rows for where the data are in the clarification materials.	Not a factual error. We acknowledge the provision of additional data/reports at the clarification stage; these have been used throughout the ERG report. However, provision of study reports is not a substitute for the full description of all relevant studies/results which should have been included in the CS, in order for the comparator and follow-up data to be seen in context.
	Please delete the statement as reported in the "description of problem" column	Please see the Natural History Results shared on February 27 (Table 2d and 3b)	Not a factual error
Page 84 of the ERG report where it states: The CS did not report any comparator results for development and progression of	Please delete the statement as reported in the "description of problem" column	Please see the Natural History results shared on February 27 (Table 2d and 3b)	Not a factual error

heart or kidney damage.			
Pg 85 of the ERG report where it states: The CS does not include any data on hyperphagia from the NIH follow-up study.	Please delete the statements as reported in the “description of problem” column	Please see the NIH Follow-Up study results shared on March 2 (Table 2a, 3b and 3c)	Not a factual error
Pg 86 of the ERG report where it states: The CS did not report any comparator results for hyperphagia and the GL/PL natural history study did not report any information about hyperphagia.	Please delete: The CS did not report any comparator results for hyperphagia	The NIH Follow-up study baseline data reflects the burden of lipodystrophy prior to metreleptin treatment and is at least as appropriate of a "comparator" as the Natural History study. Please see Table 2a in the NIH Follow-up study results shared March 2.	Not a factual error
Pg 86 of the ERG report where it states: The CS does not include any data on concomitant medication use from the NIH follow-up study.	Please delete the statements as reported in the “description of problem” column	Please see the NIH Follow-Up study results shared on March 2 (Table 2a and 4)	Not a factual error
Pg 88 of the ERG report where it states: The CS did not report any comparator results for reproductive dysfunction (from the GL/PL natural history study)	Please delete the statements as reported in the “description of problem” column	Please see the Natural History results shared on February 27 (Tables 2e and 3c)	Not a factual error
Pg 89 of the ERG report where it states: The CS did not report any comparator results for pancreatitis (from the GL/PL natural history study).	Please delete the statements as reported in the “description of problem” column	Please see the Natural History results shared on February 27 (Table 2b, 3b and 3d)	Not a factual error
Pg 89 of the ERG report where it	Please delete the statements as reported in the	Please see the Natural History	Not a factual error

states: The CS did not report any comparator results for impaired physical appearance or ability to perform activities of daily living (from the GL/PL natural history study).	"description of problem" column	results shared on February 27 (Table 2a and 3a)	
Pg 12 of the ERG report where it states: The CS (section 12.1.2, page 153) states that the comparator for the cost effectiveness analysis was standard clinical management without metreleptin, as defined in the NICE scope, (including lifestyle modifications such as diet and exercise, use of lipid lowering drugs; and medications for diabetes). **However, no data for the comparator were included in the clinical effectiveness section of the CS.**	Please either delete: However, no data for the comparator were included in the clinical effectiveness section of the CS. or change to: No data for the comparator were included in the clinical effectiveness section of the CS, however they were provided in the cost-effectiveness section and in response to clarification questions	The wording implies the data were not provided at all, either in the CS or in response to clarification questions	Not a factual error
Pg 12 of the ERG report where it states: Parameters for the standard of care arm, in the cost effectiveness analysis, were informed by a single natural history study, **which was not included in the CS.**	Please Revise: Parameters for the standard of care arm, in the cost effectiveness analysis, were informed by a single natural history study and by the pre-treatment data from the NIH Follow-up study.	The wording implies the data were not provided at all, either in the CS or in response to clarification questions. Please see Natural History results shared on February 27.	Not a factual error
Pg 13 of the ERG report where it states:	Please either delete: The clinical effectiveness sections of the CS did	The wording implies the data were not provided at all, either in the CS	Not a factual error

The clinical effectiveness sections of the CS did not include any results from control/comparator studies.	not include any results from control/comparator studies. or change to: The clinical effectiveness sections of the CS did not include any results from control/comparator studies, however they were provided in the cost-effectiveness section and in response to clarification questions	or in response to clarification questions Please see the Natural History results shared on February 27	
Pg 38 of the ERG report where it states: The CS (section 12.1.2, page 153) states that the comparator for the cost effectiveness analysis was standard clinical management without metreleptin (including lifestyle modifications such as diet and exercise, use of lipid lowering drugs; and medications for diabetes). **However, no data for the comparator were included in the clinical effectiveness section of the CS.**	Please either delete: However, no data for the comparator were included in the clinical effectiveness section of the CS. or change to: No data for the comparator were included in the clinical effectiveness section of the CS, however they were provided in the cost-effectiveness section	The wording implies the data were not provided at all, either in the CS or in response to clarification questions	Not a factual error
Pg 103 of the ERG report where it states: The natural history study, used to provide comparator data for the cost effectiveness analysis, is not used in the clinical effectiveness sections of the CS	Please delete: is not used in the clinical effectiveness sections of the CS	The wording implies the data were not provided at all, either in the CS or in response to clarification questions	Not a factual error
Pg 195 of the ERG report where it states: The natural history study,	Please delete: is not used in the clinical effectiveness sections of the CS	The wording implies the data were not provided at all, either in the CS	Not a factual error

used to provide comparator data for the cost effectiveness analysis, is not used in the clinical effectiveness sections of the CS.		or in response to clarification questions	

Issue 15 Estimation of abnormality cost

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 160 of the ERG report where it states: The ERG requested from the company to provide details of the estimation of the abnormality costs per patient. In their response to the clarification letter, the company stated that costs per inpatient hospital stay for each organ were computed using the Health Resource Group (HRG) currency codes on Table 35, which yielded values of £11,888 for heart, £16,556 for kidney, £22,104 for liver, and £1,301 for pancreas abnormality. **ERG comment:** However, it was still not clear to the ERG, how these values were derived from the HRGs.	Details were provided in question B23 (27 Feb submission documents) on the estimation of costs per patients within abnormalities but have been provided here with further detail on the calculation methods used (see 'Justification for amendment' column in this table). Based on the further information provided, please consider deleting or rewording 'However, it was still not clear to the ERG, how these values were derived from the HRGs' to "Whilst it was not clear from the CS how these values were derived from the CS, clarification was subsequently received from the company".	The cost for each abnormality (heart, kidney, liver, pancreas) are taken from NHS Reference Costs 2016 using the items and costs based on total HRG's or non-elective short-stay items, then calculating the weighted cost for each abnormality for use in the model. The heart abnormality cost has been based on the weighted average cost of total HRG currency codes: ED22A, ED22B, ED22C, ED23A, ED23B, ED23C, ED24A, ED24B, ED24C, ED25A, ED25B, ED25C, ED26A, ED26B, ED26C, ED27A, ED27B, ED27C, ED28A, ED28B, ED28C. These currency codes all refer to a coronary artery bypass (standard/complex/major), or heart valve replacement or repair. Using the total HRG weighted average cost results in a cost of £11,888.10.	Not a factual error. We would like to thank the company for these details but these details were not provided neither in the CS nor in the response to the clarification letter documents.

		Kidney abnormality cost has been based on the weighted cost of the total HRG's for transplant using: LA10Z (live kidney donor screening) with unit cost of £232.52; plus the cost of kidney pre-transplantation work-up costs using items LA11Z, LA12A, LA12B with a weighted cost of £373.44; plus cost of kidney transplant (based on codes LA01A, LA01B, LA02A, LA02B, LA03A, LA03B) at a weighted cost of £15,716.14; plus costs of examination post-transplantation using codes LA13A, LA13B, LA14Z resulting in a weighted cost of £233.69. Summing these costs (£232.52 + £373.44 + £15,716.14 + £233.69) results in a total cost of £16,555.80 which is used in the model. GA01A (Hepatobiliary Transplant, 1 year and under), GA01B (Hepatobiliary Transplant, between 2 years and 17 years), and GA01C (Hepatobiliary Transplant, 18 years and over). The number of each activity, activity unit cost and total cost were used to calculate a weighted average of £22,103.64.	

		Liver abnormality cost has been based on the weighted cost of the total HRG's for transplant using GA01A (Hepatobiliary Transplant, 1 year and under), GA01B (Hepatobiliary Transplant, between 2 years and 17 years), and GA01C (Hepatobiliary Transplant, 18 years and over). The number of each activity, activity unit cost and total cost were used to calculate a weighted average of £22,103.64. Pancreas abnormality cost has been based on the weighted cost of non-elective short stay items KA08A (Other Endocrine Disorders with CC Score 4+), KA08B (Other Endocrine Disorders with CC Score 2-2), and KA08C (Other Endocrine Disorders with CC Score 0-1). The number of FCE's and unit costs were used to calculate a weighted average of £1,301.47.	

Issue 16 Responsiveness of company to ERG requests

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Inaccurate characterization of company response on pg. 15 of the ERG report where it states:	**Rephrase:** The ERG requested that the company conduct multiple de novo statistical analyses, in order to try to resolve these	In mid-February, the ERG requested 13 de novo statistical analyses or model extensions. The	This is a non-factual error because an acceptable de-novo statistical analysis to

One of the most important concerns related to the organ impairment progression and matching methodology, which contributed directly or indirectly to a potential bias in favour of metreleptin treatment compared to SoC. The ERG requested that the company conduct de novo statistical analyses, in order to try to resolve these concerns. However, the company stated that they could not finalise this request given the timelines.	concerns and the company provided all but one of the requested additional analyses in response and stated that they could not finalise one requested analysis given the timelines.	company responded to 9 by February 27th and an additional 3 by March 2nd. Only the results of one request (which have since been completed) has not yet been communicated to the ERG.	derive transition probability estimates was not provided. Such an analysis should have used acceptable statistical methods, include important covariates and be based on plausible assumptions. Since the company did not provide such an analysis in their response to the clarification letter, this cannot be considered as a factual error. The company provided some statistical analysis/ tests for some of the concerns that the ERG had, but these analyses and their results were summarized in the ERG report, even though they were not used while deriving the transition probabilities (for organ impairment progression)
Inaccurate characterization of company response pg. 18 of the ERG report where it states: There are several concerns related to the estimation of organ impairment progression. Due to	**Rephrase:** Therefore, the ERG requested that the company conduct a de novo statistical analysis, however, the company stated that they were not able to finalise this request due to the given timelines and the ERG was not able to accommodate an extended timeline.	In mid-February, the ERG requested 13 de novo statistical analyses or model extensions. The company responded to 9 by February 27th and an additional 3 by March 2nd. Only the results of	Same as above

these issues, the ERG has substantial concerns about the appropriateness of the statistical methods used by the company. Therefore, the ERG requested that the company conduct de novo statistical analyses, however, the company stated that they were not able to finalise this request due to the given timelines		one request (which have since been completed) has not yet been communicated to the ERG.	
Pg. 151 of the ERG report where it states: "Despite a direct question of the ERG in the clarification letter (Question B13.c) the company did not provide details regarding the potential for overlap and/or correlation between attributes. For example, uncontrolled lab values for blood glucose will lead over time to retinopathy and if respondents are aware of this, it may create correlation between the two attributes.	**Revise** to omit "Despite a direct question of the ERG in the clarification letter (Question B13.c)"	The specific question asked was "Please also explain the selection process of attributes, given that several of them may be correlated." Our response described the process for selection of attributes, and we interpreted the "given that" clause a rationale for their interest in the attribute selection process and not as a separate request for our thoughts regarding how correlation of the attributes may have affected responses to the choice cards.	This is not a factual error, while selecting the attributes, potential correlation of the attributes and how they may have affected responses should have taken into consideration, as the ERG directly pointed out.
Pg. 171 of the ERG report where it states: In the updated version of the model submitted with the response to the clarification letter, the company did not include the time horizon in the sensitivity analyses	**Rephrase**: In the updated version of the model submitted with the response to the clarification letter, the company included a 90-year time horizon as part of the base case.	We did not include increased time horizon as a sensitivity but rather updated the base case time horizon to 90 years. The model also includes functionality to allow the user to specify an alternate horizon. We feel this approach was	Not a factual error. In the original model, time horizon was changed in the PSA and OWSA, however the ERG considers this approach to be wrong, since uncertainty in the time horizon and

as requested by the ERG.		responsive to the ERG's request	discount rates are part of methodological uncertainty, therefore should not be explored in PSA or OWSA, where only parametric uncertainty should be explored. In the updated model, the company correctly did not include time horizon in PSA and OWSA.

Issue 17 Misunderstanding regarding population expected to receive metreleptin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 22 of the ERG report where it states: The CS estimates of the numbers of UK patients eligible for metreleptin treatment appear low when compared to published estimates of the prevalence of LD; the number of patients currently treated divided by the estimated total population for England and Wales 26/58.38 million gives an estimated prevalence of approximately 0.45 cases/million. The reason for this discrepancy is unclear. Given that only some of the patients in England and Wales, who have LD, are currently eligible for treatment with metreleptin under the UK EAP at Addenbrooke's Hospital:	It is unclear what the 'published estimates of prevalence of LD' refers to, therefore, it is requested that the ERG consider rewording this to include the published estimate and source of estimate. It is also requested that 'The reason for this discrepancy is unclear' is removed or reworded as prevalence estimates have been based on those patients currently being treated with metreleptin in England and Wales which is expected to reflect the patient population more accurately than more general LD prevalence estimates.	1. Not all patients with LD will be treated with MET (this has been the experience at Addenbrooke's and at NIH and we expect this to continue) 2. We presume that most if not all patients in the UK will continue to be followed by Addenbrooke's as they have been for the past 10+ years.	Not a factual error

'Recombinant leptin is specifically indicated for patients with severe LD and low leptin levels (<10 µg/L). The national service will select and treat patients with leptin as is clinically indicated. The cost of leptin is expressly excluded from the funding for this service.'			

Issue 18 Model Time Horizon

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 109 of the ERG report (Table 23) where it states: No, lifetime horizon should have been considered, but the time horizon was chosen as 60 years, and not all patients were dead at the end of the time horizon.	**Rephrase**:-The time horizon was chosen as 60 years, and not all patients were dead at the end of the time horizon. The company provided an extended time horizon (90 years) in response to the ERG's request.	An extended model, including 90 years of follow-up, was submitted on March 2 in response to the ERG's request number B8 (see page 10 of Company's responses).	Not a factual error. The summary part of the ERG report is based on the original submission, the changes included in the response to the clarification letter were mentioned later in the critique part of the ERG report.
Pg. 110 of the ERG report where it states: The time horizon and the mortality calculations should be adjusted in such a way that a negligible number of patients is alive at the end of the time horizon.	**Add:** To address this consideration, the company provided an extended time horizon (90 years) in response to the ERG's request.	An extended model, including 90 years of follow-up, was submitted on March 2 in response to the ERG's request number B8 (see page 10 of Company's March responses).	Not a factual error. Again, the summary part of the ERG report is based on the original submission, the changes included in the response to the clarification letter were mentioned later in the critique part of the ERG report.
Pg. 129 of the ERG report where it states: 4. Having a substantial number of	**Revise** to acknowledge that the point was addressed in the company's clarifications	An extended model, including 90 years of follow-up, was submitted on March 2 in response to the	Not a factual error. Again, the summary part of the ERG report is based on the

patients alive (above 25%) at the end of the time horizon		ERG's request number B8 (see page 10 of Company's March 2 responses).	original submission, the changes in the response were mentioned in the critique.

Issue 19 Data source for measurement of HRQoL

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 110 of the ERG report (Table 23) where it states: The disutility values associated with disease attributes in the model were derived from a discrete choice experiment, within a sample that is argued to reflect the general population (1000 respondents). The valuation was based on some QALY estimation techniques in the literature	**Insert missing information:** Split current table entry to specify a source for "data for measurement of HRQoL": Patient quality of life data was based on a set of patient attributes extracted from patient charts as part of the NIH Follow-Up study.	The NICE reference case specifies both that quality of life data reflects patients with the condition studied and that the quality of life data are valued by members of the general public and the table omitted information regarding where the patient specific data came from.	Not a factual error. The disease attributes collected from patient charts give information on how disease attributes change in time, and how metreleptin impacts these attributes. For the ERG, this is not HRQoL data per se, but more on disease progression and natural history/ clinical effectiveness. The selection process of the disease attributes can be considered as a part of DCE.

Issue 20 Modelling of organ abnormality progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 111 of the ERG report where it states: Once real-world data are no longer available for a given patient, organ abnormality	**Rephrase:** For SoC, the cumulative number of impaired organs at baseline is assumed to match those of the treated patients, and is then extrapolated from the first cycle of the model onwards.	The statement seems to imply that real-world data are not used at all in the context of SoC, which is inaccurate.	Not a factual error. The baseline characteristics in both metreleptin and SoC arms (disease attributes, age, sex, disease type, etc.) were the

progression is extrapolated at an aggregate level (i.e. in terms of cumulative number of impaired organs), following a Markov process. For SoC, the cumulative number of impaired organs is extrapolated directly from the start of the time horizon, since the company stated that there were no patient level data on organ abnormality.			same and based on NIH Follow-up study. The data from GL/PL Natural History study was used in estimating transition probabilities for organ impairment progression. It was explained in detail in further parts of the report.
Pg. 116 of the ERG report where it states: The first KM curve in Figure 1 below represents time to develop the first organ abnormality; the second KM curve represents time to develop the second organ abnormality (given one abnormality at the baseline); the third KM curve represents time to develop the third organ abnormality (given two abnormalities at the baseline) and the last KM curve represents time to develop the fourth organ abnormality, given three abnormalities at the baseline.	**Rephrase:** […] the second KM curve represents time to develop the second organ abnormality, conditional on having developed a first either at baseline or during the study; the third KM curve represents time to develop the third organ abnormality, conditional on having developed a second either at baseline or during the study; and the last KM curve represents time to develop the fourth organ abnormality, conditional on having developed a third either at baseline or during the study.	The sample of patients included in the risk pool for each progression analysis includes both patients who start the study with a certain number of abnormalities, as well as those who achieve that number at some point during the study.	Not a factual error. The ERG thanks the company for this extra clarification, however, this was not clear neither in the company submission nor in the response documents. The ERG just expressed its interpretations, concerns and doubts during the time of the appraisal based on the evidence provided in the CS and response(s) to the clarification letter.
Pg. 119 of the ERG report where it states: The ERG had the impression that	**Revise** "This was how organ impairment was extrapolated in the model" to "This was how organ impairment was extrapolated in the	The organ abnormalities can resolve in the CE model (when supported by improved lab values),	Not a factual error. By extrapolation of organ impairment, the ERG meant

the conditions which are categorised as an organ impairment in Table 25 above were considered to be permanent, non-reversible conditions; this was how organ impairment was extrapolated in the model, as the number of impaired organs can only stay the same or increase over time. However, from the real-world data provided in the electronic model of the CS, it became clear to the ERG that these conditions could actually be reversible (i.e. in some of the cycles, the previously existent abnormalities of the kidney, pancreas and liver had resolved).	analysis of the NIH Follow-Up study and Natural History study data that was used to provide organ abnormality progression rates for the CE model."	but for the purposes of progression rate estimation, once an abnormalities of a specific organ was recorded, it was assumed to persist. E.g., a patient with a kidney abnormality only at baseline is categorized as having one abnormality and will "progress" if an abnormality of the liver, heart, or pancreas develops for the estimation of the transition rates, even if lab data supports subsequent resolution of the baseline kidney abnormality.	the extrapolation after patient level data from NIH Follow-up trial becomes unavailable. This is realized by transition probabilities, therefore, in the extrapolation process, number of impaired organs remained constant or increased in time.

Pg. 122 of the ERG report where it states: Furthermore, the ERG has doubts about the compatibility of the time to event data used for the NIH Follow-up study and for the GL/PL Natural History study	**Remove** this claim and the following two paragraphs which begin "In Figure 36 from the CS" and "The company seems to follow a different approach"	It is coincidental that the number of "at risk" patients for each progression we observe sum to 112. In both data sets patients at any point during the study with a specific number of abnormalities are "at risk" to transition to the next state. The same method is applied to both NIH and GLPL patients and, hence, the definition of time to event are identical for both samples and our recommended rephrasing on page 115 should also clarify this.	Not a factual error. The ERG thanks the company for this extra clarification, however, the ERG just expressed its interpretations, concerns and doubts during the time of the appraisal based on the evidence provided in the CS and response(s) to the clarification letter.
Pg. 127 of the ERG report where it states: Eventually the company chose to use the Cox proportional hazard model with the number of impaired organs as the only independent variable. The formal goodness of fit test results were not provided and the reasons for the selection of the model to use in the base-case were not explained.	**Omit:** The formal goodness of fit test results were not provided and the reasons for the selection of the model to use in the base-case were not explained.	Both the goodness of fit test results and the rationale for selecting the exponential model were provided in section 17.6.2.2 of the CS.	Not a factual error. Here, the ERG was referring to the lack of goodness of fit test results pertaining to the models exploring different covariates, not to the goodness of fit results for parametric survival models (exponential, Weibull, etc.) fitted on KM data.
Pg. 177 of the ERG report where it states: Furthermore, the approaches used to incorporate time to event data from the NIH follow-up study and from the GL/PL natural	**Omit**	It is coincidental that the number of "at risk" patients for each progression we observe sum to 112. The same method is applied to both NIH and GLPL patients and, hence, the definition of time to	Not a factual error. The critique was based on the judgements/interpretations of the ERG based on the limited explanation provided during the appraisal in the company

history study were incompatible.		event are identical for both samples.	submission and response to the clarification letter. The ERG is still doubtful about this extra clarification, because if the same approach had been followed for the NIH Follow-up study as in the GL/PL study, the sum of the “number at risk” would be expected to be higher than 112, which is the number of total patients in the trial. If in the NIH trial only the patients in the baseline were considered in “number at risk” figures, then sum of these “number at risk” figures would be 112. Otherwise, the sum of these figures is expected to be larger than 112, because, for instance, the patients who developed their 1st organ impairment would be considered in the “number at risk” population for the KM curve analyzing time to 1st organ impairment to time to 2nd organ impairment.

Issue 21 Mentions of bias towards metreleptin or statements that question company's good faith effort

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 120 of the ERG report where it states: Considering organ impairment improvements only for the metreleptin patients and not for the patients on SoC may well lead to a bias in favour of the metreleptin.	**Revise to note:** Company provided a sensitivity in the electronic model to allow the user to explore the impact of this assumption.	No systematic bias towards metreleptin was intended. We reflected the evidence of improvement observed among the treated patients in the NIH study and felt this was appropriate as metreleptin is not intended to be used as a substitute to SoC, and we are only trying to measure the incremental benefit/improvement with metreleptin + SoC Vs. SoC only. We have provided a sensitivity to show the impact of including organ impairment improvement vs. not.	Not a factual error. The organ impairment improvement definitions were not very clear and "no organ impairment improvement" was not considered in the base-case.
Pg. 145 of the ERG report under the header: The extrapolation method assumed for the other attributes And text including: In addition, besides the drug acquisition costs, the model only reflects the impact of discontinuation in the organ impairment progression (i.e. when a patient discontinues, metreleptin, organ progression transition probabilities for SoC will be used for that patient). The ERG considers that the	**Please revise** to include information about the extrapolation method for other attributes the company incorporated into the model, per the ERG's request. Note: While the company's method in the base case was consistent with the use of the LOCF approach across attributes, we agree with the ERG that we were not conservative enough in this approach on the treatment of the attributes other than organ abnormalities in the context of treatment discontinuation (in retrospect, we would consider an analysis relaxing this assumption to allow both partial revision to SoC values after discontinuation as well as allowing progression over time of these attributes under SoC). At the same time, a) the ERG is overly aggressive in	The LOCF approach that was used for all attributes except organ abnormalities throughout the model means that untreated patients maintain their baseline characteristics throughout the model. Most patients are unimpaired for several attributes at baseline, and thus remained unimpaired throughout the model. As LD is a progressive disease, this likely introduces a bias into the model in favor of the standard of care arm. Per the ERG's request, we implemented functionality into the model to allow for attributes other than organ abnormalities to change over time for untreated patients. While our approach is simplistic, we feel it allows for better exploration of the size of the potential bias against metreleptin that	Not a factual error. The ERG noticed that the impact of discontinuation was not incorporated in other disease attributes than organ impairment and tried to incorporate it in an exploratory analysis to demonstrate the impact of discontinuation. The approach the ERG followed for post-discontinuation was the same as the approach the company followed in modeling post-discontinuation extrapolation of organ impairment. Without evidence, the ERG considers the comments of the company on the "aggressiveness" of the ERG

impact of discontinuation should also be reflected in other disease attributes, (e.g. blood-lab values, hyperphagia, ability to work etc.). Not including the impact of discontinuation on these attributes created a bias in favour of metreleptin.	scenario 1 in assuming that with probability 1 every attribute will immediately return to baseline post-discontinuation (and a more conservative approach would assume a more uncertain switch back), and b) we were overly conservative in assuming no progression under SoC of non-organ abnormality attributes' over time. When a) and b) are considered, initial estimates of the cost-effectiveness of metreleptin, the bias in our ICER estimates doesn't appear to be meaningful. We plan to reach out to the ERG to identify the best way to share these revised analyses.	results from the LOCF choice.	exploratory scenarios or “over-conservativeness” of the company’s modeling approach of SoC non-organ impairment attributes as speculative.
Pg. 178 of the ERG report where it states: More specifically, the RWD data used to estimate important inputs for the model is not reliable (e.g. twice data updates without being able to track what was been updated and how.	**Revise to strike** "without being able to track what was been updated and how"	What was updated and how was described in the NIH report, submitted as part of the March 2nd submission. "The following data were revised post-submission: - For three patients, the following HbA1c laboratory values were revised: Patient 60, 5.6 percent for Year 2 (previously 5.3); Patient 83, 6.2 percent for Year 1 (previously 10.8); and Patient 86, 5.2 percent for Years 3 through 16 (previously 5.3). -Patient 55 is now noted as having evidence of hyperphagia at baseline (previously noted without hyperphagia pre-metreleptin	Not a factual error. These changes and data updates were not described in the main response to the clarification letter in an easily traceable, transparent way. This was expected from the company in its response to the clarification letter, and just referring to the NIH report for the changes was not sufficient, as the ERG was expected to audit the whole document, which was unrealistic considering the timelines.

		initiation). -The last known status date for the 94 patients confirmed alive is 2017-12-18 (previously last known status date was 2017-01-22). -Patient 39 is now considered to be alive as of 2017-12-18. Therefore, the end of follow-up date used for this individual is now 2017- 12-18. -Emergent issues dates were added for 5 patients with emergent heart abnormalities post-metreleptin, 42 patients with emergent kidney abnormalities post-metreleptin, and 13 patients with emergent liver abnormalities post-metreleptin, to resolve inconsistencies present for patients with unknown abnormality prior to metreleptin or multiple abnormalities post-metreleptin."	

Issue 22 Survival modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG report

Pg. 129 of the ERG report where it states: 3. Lack of face validity for the GL/PL patient's survival extrapolation results (some GL/PL patients have a more favourable life expectancy than the general UK population)	**Omit or revise** to acknowledge that the point was addressed in the company's clarifications	This concern was addressed in responses submitted to the ERG in February via the extension of the model horizon and the incorporation of a cap to ensure that the period risk of death was always the larger of the age associated risk and the disease associated risk. See response to request B9, on page 47 of the Company's February responses to the ERG's clarifications.	Not a factual error. The original submission was lacking face validity and the company's model submitted in the response to the clarification letter was acknowledged later in the critique part of the ERG report.
Pg. 133 of the ERG report where it states: Firstly, the age-adjustment procedure applied to the GL/PL natural history study patients was not clear. Secondly, **Figure 4 above suggests that patients receiving SoC live longer and the additional KM curve says nothing about the relevance of choosing an exponential distribution for the extrapolation**. Therefore, the ERG disagrees with the company's interpretation of this graph, which states: "The graph in Figure 1 shows that the exponential extrapolation is in line with this constructed KM curve from the	**Revise**: Figure 4 above suggests that patients ~~receiving SoC~~ in the Natural History Study live longer ~~and the additional KM curve says nothing about the relevance of choosing an exponential distribution for the extrapolation Therefore,~~ However, the ERG disagrees with the company's interpretation of this graph	This statement conflates the patients in the Natural History Study (whose KM curve is depicted in figure 4) with the modelled patients who receive SOC rather than metreleptin in the CE model. The KM curve for Natural History patients starts at the average age of treatment initiation (17.5 years). As the Natural History patients are typically healthier than the treated patients, the fact that the KM curve for the Natural History patients is above that of the treated patients is not surprising. This is a feature of our data that we describe it in multiple parts of the CS and responses (see CS page 271; responses pages 21, 38, 47, 48, 59,	Not a factual error. The patients in the GL/PL Natural History Study received SoC and patients in the NIH trial received metreleptin + SoC. In Figure 4, age adjusted KM curve from the Natural History was plotted alongside the KM curve from the NIH trial and it was used for validation purposes to justify exponential distribution choice for survival extrapolation by the company. The ERG just interpreted Figure 4 and also disagreed with the company that Figure 4 in the ERG report justifies the exponential extrapolation. In

Natural History study".(Response to clarification letter, page 47)		and 69 (February 27) and response page 28 (March 2)). The purpose of this graph was to show that the portion of the Natural History KM curve that extends beyond the NIH curve is within the range of mortality trends suggested by the NIH curve extrapolations. We also note that the age-adjustment approach was provided in our response to questions B9, and that the CE model allows the user to choose other distributions for extrapolation beyond the exponential distribution.	different parts of the ERG report, the differences between the baseline characteristics of the NIH trial and the GL/PL Natural History trial were acknowledged.
Pg. 134 of the ERG report where it states: The ERG considers that this approach is implausible, since the number of organs is not a fixed number throughout a patient's life, but rather a time variant parameter. The average number of impaired organs was 2.76 at the start of the NIH trial, but it was probably much higher (close to four), after 10/20 years. Therefore, the baseline survival curves do not represent a patient population whose number of organ impairments stayed fixed, hence scaling these curves based on this	**Omit** as this discussion does not accurately interpret how KM curve was shifted	2.76 was not the average number of impairments at baseline, but the average number across baseline and last observation. This was done precisely to address the concern raised by the ERG: that the number of impairments changes over the course of the trial, and that using baseline means would underestimate mortality differences. Please also note that the 2.76 value reflects the average for GL patients in the January 17 version of the NIH data and this value changed slightly in the March 2 version of the NIH data to 2.61 and this change was	Not a factual error. The ERG thanks for the extra clarification but in nowhere in the company submission, it was mentioned that 2.76 was the average number of impairments across baseline and last observation. The ERG builds its summary and critique based on the evidence in the submission and response to the clarification letter and cannot guess the underlying details of calculations if they are not explained in a transparent way.

assumption, to conditional survival curves in Figures 5.2 and 5.3, probably overestimated the difference in survival at later time points in the conditional survival curves (i.e. it is expected that after many years, the number of impaired organs will be similar in all patients, independent from the number of organs impaired at the baseline).		inadvertently not reflected in the March 2 model. As the parameter is user configurable, it should be straightforward to confirm that the model results change only slightly. Our apologies.	

Issue 23 Matching

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 137 of the ERG report where it states: Table 29: Estimated progression probabilities for the full GL/PL natural history study population (N=178) and for the matched untreated pseudo patients (N=47)	**Rephrase**: […] matched untreated patients (N=47), not "untreated pseudo patients" It also appears that the data on this table reflect the original submission and not the revised matching submitted in the March 2 clarification, and we would encourage the ERG to reference the March 2nd material instead.	"Pseudo patients" refer to observation units created from the original patient data with left-truncated observation windows. There are always as many treated patients as pseudo-patients. It also appears that the data on this table reflect the original submission and not the revised matching submitted in the March 2 clarification.	Not a factual error. The ERG considers "pseudo patients" term self-explanatory. Pseudo patients refer to the changed patient-level data from the GL/PL Natural History study. Considering March 2 material, it was mentioned above that the summary of the ERG report is based on the original submission. Additional evidence provided in response to the clarification letter were handled in the ERG critique.
Pg. 135 of the ERG report where	**Rephrase**: Untreated matched patients, not	"Pseudo patients" refer to	Same as above.

it states: Untreated matched pseudo patients (generated from the GL/PL Natural History study)	"Untreated matched pseudo patients"	observation units created from the original patient data with left-truncated observation windows. There are always as many treated patients as pseudo-patients.	
Pg. 138 of the ERG report where it states: It is not clear to the ERG how these pseudo patients were generated. The code provided by the company gave some errors and the ERG is especially concerned if the starting number of impaired organs for these pseudo patients remains the same as their starting ages increase. Omitting to update the starting number of impaired organs while updating the starting age of a pseudo patient would create a bias in favour of the metreleptin arm.	**Strike this portion of the paragraph**: "and the ERG is especially concerned if the starting number of impaired organs for these pseudo patients remains the same as their starting ages increase. Omitting to update the starting number of impaired organs while updating the starting age of a pseudo patient would create a bias in favour of the metreleptin arm. "	The number of impairments does not remain the same over the lifetime of the Natural History patients and thus will vary at the start of observation for each pseudo patient. Specifically, if a patient had 1 abnormality at age 10 and 2 abnormalities at age 12, the pseudo patient with starting age of 10 will have 1 abnormality and the pseudo patient with staring age of 12 will have 2. We apologize that this was not completely clear in our submission.	Not a factual error. The ERG thanks the company for the additional explanation/ clarification but the ERG report is based on the explanation provided in the company submission and responses to the clarification letter.
Pg. 138 of the ERG report where it states: Furthermore, it was not obvious why a weight of 0.35 was chosen for the starting age and the initial number of impaired organs in the base-case. The ERG considers this choice to be arbitrary, and the weights should reflect the relative	**Omit**	This comment pertains to an outdated method that has since been revised in the Company's responses to the ERG's requests for additional analyses.	Not a factual error. It was mentioned above that the summary of the ERG report and some of the critique points were based on the original submission. The new method based on Mahalanobis matching, provided in the response to the clarification

impact of each of the covariates on the estimated treatment effect.			document were mentioned later in the ERG report, mostly handled in the ERG critique.
Pg. 139 of the ERG report where it states: The ERG considers that insufficient interpretation of the matching results was provided. The size of the untreated matched dataset (N=47) is approximately one third of the treated patients' dataset (N=112); this suggests that an untreated patient is matched to multiple treated patients from the NIH follow-up trial. The implications of this were not discussed sufficiently in the CS.	**Omit or revise** to reflect the discussion that was provided. Additionally, please note that the specific sample sizes noted reflect the original submission and not the revised matched data that was used in the March 2nd model.	We discuss clustering standard errors because the same untreated patient contributes many pseudo-patients on page 274 of the CS (January): "Since natural history patients contribute multiple observations, standard errors at the patient level are clustered." We also discuss this on page 39 of the clarification (March 2).	Not a factual error. The ERG considers that the sentence "Since natural history patients contribute multiple observations, standard errors at the patient level are clustered." on page 274 of the CS and on page 37 of the clarification (March 2) not qualifying as sufficient discussion/ arguments. Also, it was mentioned above that the summary of the ERG report and some of the critique points were based on the original submission, additional evidence provided in response to the clarification letter were handled in the ERG critique.
Pg. 178 of the ERG report where it states: Moreover, there is a lack of clarity regarding the matching algorithm used by the company	**Strike or clarify** that this comment applies to the initial CS and was addressed in the clarifications	In response to the ERG's request number B11a, the Company used a matching method that minimizes mahalanobis distance, a well-known, commonly used method that is described in NICE DSU TSD-17.	Not a factual error. The ERG noted the new matching method and the additional clarifications submitted in the responses to the clarification letter, however there were still unclear points in the algorithm, even after the

			clarification provided, as explained in the ERG report.

Issue 24 Effect of metreleptin on progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 139 of the ERG report where it states: Independent estimation of the organ impairment transition probabilities from the treated and the matched untreated patient datasets The organ impairment transition probabilities for the treated and the matched untreated patients were estimated from different datasets, independently. The ERG noted that the CS did not include any sort of justification of this approach, and questions why the treatment effect was not estimated from a pooled dataset.	**Revise** to acknowledge the company's provision of covariate adjusted analyses within the pooled data set in response to question B3.e.3 (as mentioned later on this page)	Revise to acknowledge the company's provision of covariate adjusted analyses within the pooled data set in response to question B3.e.3 (as mentioned later on the same page of the ERG report)	It is corrected. The following sentence is added at the end of the paragraph: "*In response to the clarification letter, the company provided some analyses on the pooled dataset."*
Pg. 139 of the ERG report where it states: Furthermore, it is not clear if the treatment shows a benefit for patients with a low number of organ impairments. In the covariate adjusted analyses conducted on the pooled dataset (NIH follow-up and the matched	**Omit**	The results show a significant coefficient on treatment for the transition from 1 to 2 organ abnormalities, while findings are noisier for the 2 to 3 and 3 to 4 transitions. This statement seems to suggest the opposite pattern in statistical significance.	Not a factual error. The ERG tried to interpret the results from the pooled dataset analyses the company has conducted, it seems the interpretation differs.

untreated) provided in B3.e.3 (Question B3.e.3, Response to clarification letter, pages 40-43),39 the treatment was not a significant covariate in most of the analyses.			

Issue 25 DCE Approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 151 of the ERG report where it states: The key issue is that the use of DCE to directly obtain disutility values for heath states is still in its infancy.	**Rephrase** to clarify that this is the ERG's opinion. A small sampling of DCE publications reflecting its use in health state valuation: **1)** Bansback, N., Hole, A. R., Mulhern, B., & Tsuchiya, A. (2014). Testing a discrete choice experiment including duration to value health states for large descriptive systems: addressing design and sampling issues. *Social Science & Medicine, 114,* 38-48. **2)** Gärtner, F. R., de Bekker-Grob, E. W., Stiggelbout, A. M., Rijnders, M. E., Freeman, L. M., Middeldorp, J. M., ... & van den Akker-van, M. E. (2015). Calculating Preference Weights for the Labor and Delivery Index: A Discrete Choice Experiment on Women's Birth Experiences. *Value in Health, 18*(6), 856-864. **3)** Gu, N. Y., Botteman, M. F., Gerber, R. A.,	Extensive literature on using DCE to elicit health states.	This is not a factual error, but a difference in point of view between the ERG and the company. The ERG agrees with the company that a large body of literature exists where DCE is used to value health states. However, various methodological issues still exist. Possibly as a result of this, DCE based utilities are not (yet) used in health economic modelling, hence the ERGs qualification that the use of DCE for health state utilities is still in its infancy.

	Ji, X., Postema, R., Wan, Y., ... & van Hout, B. (2013). Eliciting health state utilities for Dupuytren's contracture using a discrete choice experiment. *Acta orthopaedica*, *84*(6), 571-578. 4) King, M.T., et al. "Australian Utility Weights for the EORTC QLU-C10D, a Multi-Attribute Utility Instrument Derived from the Cancer-Specific Quality of Life Questionnaire, EORTC QLQ-C30" PharmacoEconomics 36 (2018) **5)** Norman, R., Viney, R., Brazier, J., Burgess, L., Cronin, P., King, M., ... & Street, D. (2014). Valuing SF-6D health states using a discrete choice experiment. *Medical Decision Making*, *34*(6), 773-786. 6) Stolk EA, Oppe M, Scalone L, Krabbe PF. Discrete choice modeling for the quantification of health states: the case of the EQ-5D. Value in Health. 2010 Dec 1;13(8):1005-13.		

Pg. 152 of the ERG report where it states: The survey is very long and complex, with 12 attributes being shown per card. This raises questions regarding the respondent cognitive burden of the task. From the information provided by the company it is not clear if a check for respondent burden was included, through a pre-test for example, or post-hoc by checking consistency between the first six choice sets and the last six.	**Omit**: "From the information provided by the company it is not clear if a check for respondent burden was included, through a pre-test for example, or post-hoc by checking consistency between the first six choice sets and the last six."	We included the following in response to clarification question B13a on 27th Feb, which explicitly mentions that the survey included a check for consistency: "The main motivation for a Partial Profile Design is the total number of attribute levels, as one choice card will not be able to fit all attribute levels. There were 14 choice cards presented to respondents (12 of which were used to infer utilities while 2 were used to test the consistency of responses)." More than 80% of respondents responded consistently.	Not a factual error. The ERG acknowledges that the text provided by the company indeed states that consistency of responses was checked. The company however did not present the outcome of that test, nor the actual information regarding the test and the software output. So, we thank the company for reporting the percentage consistency here.
Pg. 153 of the ERG report where it states: The company used a simple additive model to estimate the QALY weights. In this model, the intercept was excluded, and the company referred to Viney et al. 2014 as justification.1, 84 However, whilst Viney et al. indeed report that the impact of including an intercept on the calculated QALY weights was negligible in their study, this does	**Revise:** The company used a simple additive model to estimate the QALY weights. In this model, the intercept was excluded, and the company discussed this decision in the ERG's request for clarification and also provided Viney et al. 2014 as an example of this approach in the literature ~~justification.1, 84 However, whilst~~ Viney et al. indeed report that the impact of including an intercept on the calculated QALY weights was negligible in their study, a finding that largely holds in the companies study as well.~~, this does not provide any justification for omitting the intercept in general. Instead, the validity of such~~	We did, in fact, test this in the current study and report the results in page 235 of the original submission, in section 17.5.2.5: "The intercept was also excluded in Viney, et al (2014), who report that its impact on the calculated QALY weights was negligible. The same applied to our case, except for the progression of organ abnormality coefficient, the magnitude of which changed by 20% across the two estimation	The ERG did indeed miss the implication of the text from the company that they tested for the intercept exclusion as well. The text will be changed as suggested by the company

not provide any justification for omitting the intercept in general. Instead, the validity of such choice should have been tested separately in the current study.	~~choice should have been tested separately in the current study.~~	approaches. However, the contribution of this single coefficient to the overall study conclusions was negligible."	
Pg. 178 of the ERG report where it states: DCE classifies health states far more often below zero than TTO and produces lower average health state values.	**Omit**	It is unclear what evidence serves as a buttress for this claim. At least one published study finds the opposite result: Stolk et al. (2010) set out to compare DCE and TTO EQ-5D health states and conclude that "[although] modeled DC data broadly replicated the pattern found in TTO responses, the DC consistently produced higher values." (Stolk et al. (2010) pp. 1005).	Below are two example of studies that showed the issue of health states worse than death. Viney et (Health Econ. 2014 Jun;23(6):729-42) found 33% of the EQ-5D states to be worse than death using DCEduration, compared to 14% using TTO. Gu et al (Health Econ. 23: 1098–1114, 2014) reported that about half of the EQ-5D-5L states received a negative value using DCEduration.
Pg. 178 of the ERG report where it states: The most striking unresolved methodological issue relates to the fact that DCE classifies health states far more often below zero than TTO and produces lower average health state values. This was indeed observed in the	**Omit**	It is impossible to make this claim in light of the fact that we only provide estimates from a DCE, and estimates from a TTO are not available for lipodystrophy attributes.	The company is correct that these 2 issues should not have been linked together. This text been changed to: *“The most striking unresolved methodological issue relates to the fact that DCE classifies health states far more often*

results of the current DCE study.			*below zero than TTO and produces lower average health state values. Moreover, the face validity of the DCE based disutilities is low, given the derived average QoL utility for SoC of 0.03. This implies that the average patient with lipodystrophy not receiving metreleptin values his/her health state as very close to death, which seems highly unlikely."*

Issue 26 CE modelling choices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 155 of the ERG report where it states: However, there are several attributes that the company mentioned as having impact on the patient's quality of life, which were not included in the economic analyses without further justification.	**Strike the phrase** "without further justification"	We acknowledged that these attributes were not included in the model due to a lack of data regarding their prevalence in the NIH treated patients in response to question B4b, in the clarification letter submitted on 27th February.	Last two sentences were changed to the sentence below to address the company's concerns: "*However, there are several attributes that the company mentioned as having impact on the patient's QoL, which were not included in the economic analyses (pain, depression, retinopathy, neuropathy, amputation), due to lack of data, according to the company."*

Issue 27 CE modelling choices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg. 156 of the ERG report where it states: These errors led to inconsistent results, for instance, if the number of organ impairments of a patient at a given cycle is 4, the conditional probability for having a pancreas impairment would be equal to 1 (as well as having a heart, a liver or a kidney impairment). However, the formula used in the metreleptin arm, due to the errors in conditional probability calculations, provides incorrect estimates, for instance for some organs a probability value that is less than 1 and for the others a probability value that is more than 1.	**Omit.**	These these weights do not represent probabilities, but instead apportion the number of estimated abnormalities across the four organ systems in order to apply utility decrements and costs. This is necessary due to our decision to track only number organs with abnormalities and not the specific organs impaired after the end of the real-world data. For a given estimate of total impairments, let's say 2.5, we derive weights that sum up to this number for each organ impairment according to the distribution of impairment at baseline. For example, if liver accounts for 60% of baseline impairment, while kidney, heart and pancreas account for 20%, 10% and 10%, respectively, a weight of 1.5 (2.5 x 60%) is assigned to liver, while the remaining organs are assigned weights of 0.5, 0.25 and 0.25. Notice that the weight assigned to liver is greater than 1 (as the ERG observed), but should not be interpreted as a conditional probability. Please also note that our	Not a factual error. We thank the company for the additional clarification but the current weighting interpretation of the company still leads to inconsistencies and include programming errors.

		simplification is the cause of the discrepancy noted by the ERG and we acknowledge that their correction of this approach is appropriate.	
Pg. 164 of the ERG report where it states: Instead of using 0.47% obtained from the matched untreated population from the GL/PL natural history study, the company used the estimate for the metreleptin patients from the NIH follow-up study (2.19%) in the model.	**Strike or rephrase** to say the ERG does not agree with the company's modelling choice.	The current phrasing implies that the 2.19% was used in error. In the March 2nd clarification, we specify why we use the same transition rate for both treated and SoC patients transition probabilities, in response to question B3. "The treatment indicator is significant for the 1 to 2 transition and directionally correct and close to significant for the 2 to 3 transition. The 3 to 4 transition does seem to be affected by censoring and the apparent lower rate in the Natural History patients appears to be due to censoring rather than death. To account for this, we use the same transition rate for both treated and SOC patients in the CE model (2%)." We acknowledge that our discussion was not very clear. What we were trying to say is that in the Natural History study, death is a competing risk for patients with 3 organ abnormalities, and once a combined endpoint of "progression or death" is examined, we see that natural history patients are more likely to move from 3 abnormalities to 4 abnormalities	The paragraph is changed to below to address the company's concerns: "*It should be noted that in the updated electronic model, for the SoC arm, the ERG noticed that, instead of using 0.47% obtained from the matched untreated population from the GL/PL natural history study, the company used the estimate for the metreleptin patients from the NIH follow-up study (2.19%) in the model, arguing that the lower rate from GL/PL Natural study is heavily affected by censoring. The ERG does not agree with this choice and uses previous estimates.* "

		or death than are treated patients.	

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Metreleptin for treating lipodystrophy

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check. The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
12	Correction of transcription error: 'In study FHA101, mean actual change from baseline to Month 12/LOCF for HbA1c was -1.2% (95% CI: -4.3 to 2.0) for GL patients and -0.9% (95% CI: 95% CI: -1.4 to 0.4) for patients in the PL subgroup.' To 'In study FHA101, mean actual change from baseline to Month 12/LOCF for HbA1c was -1.2% (95% CI: -4.3 to 2.0) for GL patients and -0.8% (95% CI: -2.5 to 0.9) for patients in the PL subgroup.'
36	Correction of transcription error: '17/66 (25.8%) of GL patients' to '15/66 (22.7%) of GL patients'
36	Correction: 'PL patients' to 'PL subgroup patients'
36	Sentence deleted: 'The clinical effectiveness section of the CS did not include any subgroup data for genetic and acquired LD syndromes.'
80	Correction of typographical error: 'p = 0/801' to 'p=0.801'
86	Correction: 16/38 (68.2%) to 16/38 (42.1%)
88	Correction: 'Over the whole observation period, 2/15 (13.3%) of female GL patients and 15/41 (36.6%) of female PL patients were found to have reproductive dysfunction.' to 'Over the whole observation period, 11/33 (33.3%) of female GL patients and 34/86 (39.5%) of female PL patients were found to have reproductive dysfunction.'
139	Sentence added: "In response to the clarification letter, the company provided some analyses on the pooled dataset."
153	The paragraph is changed as suggested by the company, to acknowledge that the company tested for the intercept exclusion: "The company used a simple additive model to estimate the QALY weights. In this model, the intercept was excluded, and the company referred to Viney et al. 2014 as an example of this approach in the literature .[1, 84] Viney et al. indeed report that the impact of including an intercept on the calculated QALY weights was negligible in their study, a finding that largely holds in the company analyses as well."
155	Last two sentences were changed to the sentence below to address the company's concerns: "However, there are several attributes that the company mentioned as having impact on the patient's QoL, which were not included in the economic analyses (pain, depression, retinopathy, neuropathy, amputation), due to lack of data, according to the company."
164	The paragraph is changed to below to address the company's concerns: "It should be noted that in the updated electronic model, for the SoC arm, the ERG noticed that, instead of using 0.47% obtained from the matched untreated population from the GL/PL natural history study, the company used the estimate for the metreleptin patients from the NIH follow-up study (2.19%) in the model, arguing that the lower rate from GL/PL Natural study is heavily affected by censoring. The ERG does not agree with this choice and uses previous estimates. "
178	The text is corrected to below to address the company's concerns: ""The most striking unresolved methodological issue relates to the fact that DCE classifies health states far more often below zero than TTO and produces lower average health state values. Moreover, the face validity of the DCE based disutilities is low, given the derived average QoL utility for SoC of 0.03. This implies that the average patient with lipodystrophy not receiving metreleptin values his/her health state as very close to death, which seems highly unlikely.""

The ERG notes some deviations from the final agreed NICE scope. Briefly, these include:

- The CS (section 12.1.2, page 153) states that the comparator for the cost effectiveness analysis was standard clinical management without metreleptin, as defined in the NICE scope, (including lifestyle modifications such as diet and exercise, use of lipid lowering drugs; and medications for diabetes). However, no data for the comparator were included in the clinical effectiveness section of the CS.
- The clinical effectiveness section of the CS focuses primarily on metabolic outcome measures; the CS includes no data or only very limited data for the clinical or patient-perceived outcomes specified in the NICE scope. No data are provided on liver cirrhosis, complications of diabetes, organ damage (including heart and kidneys) or effects on appearance. Mortality and pancreatitis are only reported where these are considered to be adverse effects of treatment or, in the case of pancreatitis, discontinuation of treatment.

The ERG recognises that no comparative studies of metreleptin versus standard care are available and that, in such cases, cost effectiveness analysis requires an indirect comparison between treatment and comparator studies. However, where indirect comparisons are used, it is essential that the same rigorous approach to identifying, selecting and reporting studies is applied for both intervention and comparator studies. There are serious problems with the identification, selection and reporting of comparator data in the CS. No systematic attempts to identify comparator studies and no selection criteria for such studies are reported. Parameters for the standard of care arm, in the cost effectiveness analysis, were informed by a single natural history study, which was not included in the CS.

The ERG has extracted additional data on clinical/patient-perceived outcomes from a short report of a follow-up study to the main study included in the CS, which was provided in response to clarification questions. This study was used in the cost effectiveness analyses, but was not included in the clinical effectiveness section of the CS.

1.4 Summary of clinical effectiveness evidence submitted by the company

Single arm, observational studies of metreleptin treatment found improvements in metabolic abnormalities from baseline to month 12 of treatment in patients with GL and in the subgroup of patients with PL who had similar metabolic disturbances to those seen in patients with GL (PL patients with leptin level <12 ng/ml with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L).

- In study NIH 991265/20010769, mean actual change in HbA_{1c} to Month 12/LOCF was -2.2% (95% CI: -2.7 to -1.6, p<0.001) for GL patients and -0.9% (95% CI: -1.4 to -0.4, p<0.001) for patients in the PL subgroup.
- In study FHA101, mean actual change from baseline to Month 12/LOCF for HbA_{1c} was -1.2% (95% CI: -4.3 to 2.0) for GL patients and -0.8% (95% CI: -2.5 to 0.9) for patients in the PL subgroup.

In study NIH 991265/20010769, mean percent change in triglycerides to Month 12/LOCF was -32.1% (95% CI: -51.0 to -13.2, p=0.001) for the GL group and -37.4%

ERG comment: The latest available information (09/03/2018) is that: [redacted]

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

The population included in the clinical effectiveness sections of the CS relates to people with generalised and partial lipodystrophies.

A subgroup of the partial lipodystrophy population is also described (patients with baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L). The CS describes this subgroup as related to the original EMA licenced indication, which was for adults and children over two years of age with CGL or AGL, and adults and children over two years of age with FPL or APL characterised by leptin levels <12 ng/ml with triglycerides ≥5.65 mmol/L and/or HbA_{1c} ≥6.5%, uncontrolled on standard therapy.

The CS (Table A1, pages 19-20) describes a further population of interest, based on EMA day 180 questions: adults and children aged six years and over, with CGL or AGL; adults and children aged 12 years and over, with FPL or APL characterised by leptin levels <12 ng/ml with triglycerides ≥5.65 mmol/l and/or HbA_{1c} ≥8%. The studies included in the clinical effectiveness section of the CS appear to have included GL patients <2 years of age and some patients in the PL subgroup with leptin levels >12 ng/ml, triglyceride levels <5.65mmol/ml and HbA_{1c} <6.5%. Five of the 66 GL patients included in the NIH 991265/20010769 were under six years of age and one was under two years of age, 40/66 (60.6%) of GL patients and 16/31 (51.6%) of PL subgroup patients had triglyceride levels <5.65 mmol/L, and 15/66 (22.7%) of GL patients and 2/31 (6.5%) of PL subgroup patients had HbA_{1c} <6.5%. None of the patients in the FH101 study were under six years of age, however, 6/9 (66.7%) of GL patients and 6/7 (85.7%) of PL subgroup patients had triglyceride levels <5.65 mmol/L, and 3/9 (33.3%) of GL patients and 1/7 (14.3%) of PL subgroup patients had HbA_{1c} <6.5%.[37, 38]

ERG comment: The extent to which the population included in the clinical effectiveness sections of the CS is consistent with licenced indication for metreleptin remains unclear; at the time of submission of the ERG report, metreleptin does not yet have a UK licence for the treatment of LD syndromes. The latest available information (09/03/2018) suggests that: [redacted]

Persistence of change in HbA1c and triglycerides over time

The CS[37] reports some information about longer term (up to 36 months) changes in HbA_{1c} and triglycerides in patients on metreleptin treatment. Least-squares mean (LS mean) changes from baseline in HbA_{1c} in the GL group based on a mixed model repeated measures (MMRM) analysis were -2.3%, -2.1% and -1.5% at Months 12, 24 and 36, respectively.[1, 37] The overall MMRM analysis showed a statistically significant decrease from baseline for GL patients with an LS mean change of -1.4%

($p<0.001$). Results were similar in the PL subgroup with LS mean changes in HbA_{1c} of -0.9%, -1.3%, and -1.0% at Months 12, 24, and 36 and an overall LS mean change of -0.6% ($p<0.001$).[1, 37]

In the GL group, LS mean percent changes from baseline in triglycerides were -48.3%, -22.6% and -40.6% at Months 12, 24, and 36, respectively; based on the overall MMRM analysis, the LS mean change in triglycerides was -22.4% ($p<0.001$). For the PL subgroup (excluding data from the 'outlier' patient described previously), LS mean percent changes in triglycerides were -36.2%, -31.7%, and -13.7% at Months 12, 24 and 36, respectively, with an overall LS mean change of -18.6% ($p=0.004$).[1, 37]

ERG comment: Data for the overall PL population (not included in the CS) indicated no statistically significant change in triglyceride levels over time. The LS mean (SEM) percentage change values were as follows: month 12 = -16.7 (8.62), p = 0.054; month 24 = -9.4 (16.41), p = 0.566; month 36 =4.4 (17.53), p = 0.801; overall MMRM = -8.3 (5.46), p=0.131.[37]

Liver function (hepatic enzymes), liver pathology

Data from the NIH 991265/20010769 study,[1, 37] suggest that metreleptin treatment may be associated reductions in hepatic enzymes. In the 41 GL patients with hepatic data available, the mean (SD) changes, in ALT and AST, from baseline to month 12 of treatment were -53.1 (126.56) U/L and -23.8 (142.38) U/L, respectively. Reductions were smaller for the PL subgroup (-5.0 (11.95) and -6.0 (14.77) for ALT and AST, respectively) and for the overall PL group (-0.4 (26.95) and -5.1 (21.06) for ALT and AST, respectively. Full results for hepatic enzymes are provided in Table 15 below, reproduced from the CS (CS, Table C22, pages 90-92).[1] No assessments of statistical significance were presented.

Similarly, the NIH follow-up study states that 'improvement in hyperphagia is determined by improvement as indicated in post-metreleptin notes' and specifies that patients must have at least one year of post-metreleptin data in order to be included in the improvement count.[46] Based on this definition, 47 (89%) of the 53 GL patients and 25/26 (96%) of PL patients who had hyperphagia at baseline and who had at least one year of post-metreleptin data were classified as having experienced improvements in hyperphagia.[46] Whilst these results appear to indicate that metreleptin treatment is associated with improvements in hyperphagia, it should be noted that no objective measures of hyperphagia were reported and no details were provided about the nature of the hyperphagia information recorded in notes.

ERG comment: The CS did not report any comparator results for hyperphagia and the GL/PL natural history study did not report any information about hyperphagia.[40]

Concomitant medication use

The CS included some information, from the NIH 991265/20010769 study, about discontinuation of insulin, oral antidiabetics, or lipid-lowering therapies following initiation treatment with metreleptin.[1, 37] Sixteen (41%) of 39 patients with GL who were receiving insulin at baseline were able to discontinue insulin use after starting metreleptin and seven (22%) of 32 patients who were receiving oral antidiabetic medications at baseline were able to discontinue use of these drugs. Among the 34 patients who were receiving lipid-lowering therapies at baseline, eight (24%) were able to discontinue these medications.[1, 37] In the PL subgroup, one patient was able to discontinue the use of oral antidiabetic medications and one was able to discontinue the use of lipid-lowering therapies.[1, 37]

ERG comment: The CS also states that: 'Many of these patients could discontinue the use of these therapies within the first 12 months of metreleptin treatment.' However, no times to discontinuation are reported.

The CS does not include any data on concomitant medication use from the NIH follow-up study. The study report for the NIH follow-up study,[46] reported that 57/68 (83.8%) of GL patients and 43/44 (97.7%) of PL patients were on anti-diabetic medication (insulin or oral anti-diabetics) at baseline.[46] A new anti-diabetic medication was initiated (defined as two or more fills of a medication not present at baseline), after the start of metreleptin treatment, in 54/68 (79.4%) of GL patients and 36/44 (81.8%) of PL patients.[46] The equivalent data for lipid lowering medication showed that 28/68 (41.2%) of GL patients and 30/44 (68.2%) of PL patients were on lipid-lowering medication (statin and/or fibrates) at baseline.[46] A new lipid-lowering medication was initiated (defined as two or more fills of a medication not present at baseline), after the start of metreleptin treatment, in 18/68 (26.5%) of GL patients and 27/44 (61.4%) of PL patients.[46] Medication discontinuation was defined as a 12-month period without any medication prescription fills and included both baseline medications and medications initiated after the start of metreleptin treatment; 41/64 (64.1%) of GL patients and 15/44 (34.1%) of PL patients were able to discontinue antidiabetic medications.[46] Most discontinuations were for bolus insulin or metformin, only two GL patients discontinued basal insulin or insulin + metformin.[46] With respect to lipid-lowering medication, 19/35 (54.3% of GL patients and 16/38 (42.1%) of PL patients were able to discontinue lipid lowering

study included seven female patients with severe LD; five of these patients had intact reproductive systems and only one was cycling normally at the start of metreleptin treatment, but all five had normal menses by the fourth month of treatment.[58] The results from these two publications were not included in the CS.

The NIH follow-up study[46] also reports information about the effects of metreleptin treatment on female reproductive dysfunction. The report defined disruption to the female reproductive system as the presence of irregular menstruation or polycystic ovary syndrome (PCOS). Female patients are not considered to have disruption to female reproductive function if they are experiencing menopause, are prepubescent, or had surgical removal of reproduction organs. At baseline, 21/27 (78%) of relevant female GL patients and 24/29 (83%) of relevant female PL patients were classified as experiencing reproductive dysfunction.[46] Twelve (57%) of the 21 effected GL patients and eight (33%) of the 24 effected PL patients were reported as having post-metreleptin improvement ('improvement in any of irregular menstruation or PCOS').[46] However, no definition of the criteria used to determine improvement was provided.

The CS did not report any comparator results for reproductive dysfunction (from the GL/PL natural history study); a study report was provided in response to clarification questions and this report includes information about female reproductive dysfunction in LD patients.[40] This report included information on the number of female patients with reproductive dysfunction (including amenorrhea, menstruation <6 times per year, pregnancy loss, infertility or subfertility, ovarian cysts, and PCOS) at baseline, (see Section 4.2.1, Table 6). Over the whole observation period, 11/33 (33.3%) of female GL patients and 34/86 (39.5%) of female PL patients were found to have reproductive dysfunction.[40] Using the reported data for the baseline period and the whole observation period, it is possible to calculate the proportion of patients, who did not have reproductive dysfunction at baseline, but developed problems during the follow-up period (after GL/PL diagnosis). Of the 13 female GL patients who did not have reproductive dysfunction at baseline, nine (69.2%) developed reproductive dysfunction during follow-up and 19/26 (73.1%) of female PL patients who did not have reproductive dysfunction at baseline developed problems during follow-up.

Pancreatitis

The clinical effectiveness section of the CS does not include any information about the effects of metreleptin treatment on pancreatitis; pancreatitis is only reported as an adverse event occurring subsequent to metreleptin withdrawal (CS, section 9.7.2.5, page 114).

ERG comment: The NIH follow-up study[46] reports information about the effects of metreleptin treatment on pancreatitis. A patient was considered to have pancreatitis at baseline if they had ≥1 episodes of pancreatitis in the one year prior to metreleptin initiation.[46] At baseline, 21/63 (31%) of GL patients and 23/44 (52%) of PL patients had a history of pancreatitis.[46] Improvement in pancreatitis was defined as no recorded episodes of pancreatitis post-metreleptin initiation or only episodes of pancreatitis which were due to non-compliance.[46] Based on these criteria, 20/21 (95%) of effected GL patients and all effected PL patients experienced improvements in pancreatitis on metreleptin treatment. These data were not included in the CS, but are of particular importance given the identified risk of pancreatitis

arbitrary, and the weights should reflect the relative impact of each of the covariates on the estimated treatment effect.

Independent estimation of the organ impairment transition probabilities from the treated and the matched untreated patient datasets

The organ impairment transition probabilities for the treated and the matched untreated patients were estimated from different datasets, independently. The ERG noted that the CS did not include any sort of justification of this approach, and questions why the treatment effect was not estimated from a pooled dataset. In response to the clarification letter, the company provided some analyses on the pooled dataset.

Lack of interpretation of the results

The ERG considers that insufficient interpretation of the matching results was provided. The size of the untreated matched dataset (N=47) is approximately one third of the treated patients' dataset (N=112); this suggests that an untreated patient is matched to multiple treated patients from the NIH follow-up trial. The implications of this were not discussed sufficiently in the CS.

Furthermore, it is not clear if the treatment shows a benefit for patients with a low number of organ impairments. In the covariate adjusted analyses conducted on the pooled dataset (NIH follow-up and the matched untreated) provided in B3.e.3 (Question B3.e.3, Response to clarification letter, pages 40-43),[39] the treatment was not a significant covariate in most of the analyses.

Given the lack of discussion on the "no unobservable confounding" assumption, the arbitrary selection of covariates (omitting many other observable confounders such as the type of organ impaired), the arbitrary selection of the methods, and how the treatment effect is estimated from the matched datasets, the ERG considers that the clinical inputs (resulting from the matching and the corresponding survival and organ impairment transition probability estimation exercises) used in the cost-effectiveness part of the submission are not trustworthy.

5.3.3.4 Other attributes (blood-lab and attributes other than organ damage)

In the extrapolation of blood-lab attributes (i.e. HbA_{1c} and triglyceride values), for the metreleptin arm, real-world data from the NIH follow-up study are used directly, to populate the model until the last time data are available. When real-world data become unavailable, the last observation carried forward (LOCF) method is used to extrapolate blood-lab attributes and the last observed data is assumed for all the periods until the end of the time horizon. For the SoC arm, the baseline blood-lab attribute values from the NIH follow-up study are assumed to remain unchanged throughout the whole time horizon.

In the extrapolation of the remaining attributes other than blood-lab and organ damage (i.e. hyperphagia, ability to work, reproduction, physical progression and fast progression), for the metreleptin arm, in some of the patients, some of the disease attributes are assumed to improve from the baseline value. This improvement is assumed from the first cycle and onwards until the end of the time horizon. It is stated that these improvements were based on the observed

different disutility weights for male and female patients, given the current design of the choice cards.

In the company submission, no information was provided regarding the experimental design of the DCE. Thus, the ERG asked for additional information in the clarification letter (Question B13.b). In their response, the company explained that a Partial Profile Design was used, to allow for the option of not showing all attributes on each choice card, but rather a subset of 12 attributes. However, no further information was provided. So, it is not evident if a (Bayesian) D-efficient design was used? Neither is it clear whether priors were used and if so, why and which. The ERG would also have preferred to receive details on the correlation matrix as the question may be raised to which extent the DCE-values are based on preference values or are (partially) a product of correlation in the design itself.

Using a sound experimental design for a DCE is of key importance to find valid preference values and the lack of details provided by the company make it very difficult to assess the design used by the company.

MNL model

The company explained in the CS that a multinomial logit model was used to analyse the choice data. As the choices were always between two alternatives, this reduces to a logit model. These models have three strong assumptions: independence from irrelevant alternatives (or IIA) assumption, the identical and independent distribution (IID) assumption for the error terms and preference homogeneity. No information was provided in the CS or in the response to the clarification letter regarding any formal testing to check if these assumptions are satisfied. A mixed logit model which allows for preference heterogeneity should at the very least have been tested. It is quite possible that this alternative model would have had a substantial impact on the results. Thus, the model used by the company is most likely too simplistic for decision making.

The company decided to use a model that did not include age of the hypothetical patient as attribute. Most likely, age had an impact on the weights of other attributes (through at least a two-way interaction) and thus the ERG does not agree with the interpretation given by the company: "Excluding age implied that the analysis effectively calculated the QALY weights for a hypothetical patient of average age."[1]

The company used a simple additive model to estimate the QALY weights. In this model, the intercept was excluded, and the company referred to Viney et al. 2014 as an example of this approach in the literature .[1, 84] Viney et al. indeed report that the impact of including an intercept on the calculated QALY weights was negligible in their study, a finding that largely holds in the company analyses as well.

Attribute and level selection

The selection of attributes and levels has not been determined with the target population. A pilot testing or at least asking patients which key symptoms are deemed important would have

Table 1: Utility decrements used in the cost effectiveness analyses

Attribute	Mean value	Standard error	Source
Heart Abnormality	-0.19	0.047	Company DCE and assumptions[1]
Liver Abnormality	-0.15	0.038	
Pancreas Abnormality	-0.13	0.032	
Kidney Abnormality	-0.13	0.028	
Hyperphagia	-0.11	0.015	
Disruption to female reproductive function	-0.06	0.064	
Loss of ability to perform work / school	-0.25	0.047	
Impaired Physical Appearance	-0.10	0.025	
Triglycerides: Achieved Goal (<=200 mg/dL)	0.00	NA	
Triglycerides: Partial Response (>200 mg/dL, <=500 mg/dL)	-0.05	0.012	
Triglycerides: No Response (>500 mg/dL)	-0.11	0.028	
HbA_{1c}: Hypoglycemia	-0.01	0.004	
HbA_{1c}: Achieved Goal (>4.0, <=7.0)	0.00	NA	
HbA_{1c}: Partial Response (>7.0%, <=8.0%)	-0.08	0.02	
HbA1C: No Response > 8.0%	-0.18	0.045	
Source: Table D37 and the electronic model in the CS[1]			

ERG comment:

The utility decrements derived from the company's DCE were used in the economic analyses since the characteristics valued by the DCE were similar (but not identical) to those collected in the NIH study. The effect of changes in utility decrement values was explored via sensitivity analyses. However, there are several attributes that the company mentioned as having impact on the patient's QoL, which were not included in the economic analyses (pain, depression, retinopathy, neuropathy, amputation), due to lack of data, according to the company.

Despite the significant number of adverse events described in Section 5.3.3.5, only hypoglycaemia was included in the cost effectiveness analysis as an adverse event (with an associated utility decrement). No effort has been made to quantify the possible impact of other adverse events on patients' quality of life.

The CS (CS, Section 12.1.3, page 151) states that the true utility decrement associated with hyperphagia is likely to be underestimated since, according to the company, the "DCE cannot fully encompass the patient experience of such a unique aspect of the disease".[1] To quantify the impact of the utility decrement associated with hyperphagia on the cost effectiveness analyses, the company presented a scenario where this decrement was doubled. For further discussion on the utility decrement associated with hyperphagia the company refers to Section

Estimated progression probabilities for the original model - Matched GL/PL Natural History Patients (N=47)			
Progression event	**Estimated progression probability**	**Number of patients at risk**	**Number of progressions**
0 to 1	0.089	36	36
1 to 2	0.173	42	39
2 to 3	0.123	44	36
3 to 4	0.062	36	16
Sources from top to the bottom: from Table 71 from the CS; Table 7 from the second tier of the response to the clarification letter; from Table 78 from the CS and Table 9 from the second tier of the response to the clarification letter.[1, 39]			

It should be noted that in the updated electronic model, for the SoC arm, the ERG noticed that, instead of using 0.47% obtained from the matched untreated population from the GL/PL natural history study, the company used the estimate for the metreleptin patients from the NIH follow-up study (2.19%) in the model, arguing that the lower rate from GL/PL Natural study is heavily affected by censoring. The ERG does not agree with this choice and uses previous estimates.

Furthermore, the ERG identified another programming error, which affected the company submission base-case. Due to the eligibility criteria of the original expected licensed indication, the company should have taken severe PL patients with triglycerides > 500 mmol/l and/or HbA_{1c} > 8% into account. However, the company applied the thresholds in a wrong way and applied these minimum thresholds as maximum thresholds. This wrong implementation of the license indication had excluded several severe PL patients from the base-case analysis. The ERG corrected these errors and present the corrected CS base-case analyses in Section 6.

5.4 Headline results reported within the company's submission

This section summarises the results of the economic analyses as presented by the company in its latest response to the clarification letter with the updated electronic model.[39] The company considered four different base case scenarios depending on the size of the vial and the price used for metreleptin. Thus, the results of the first base case scenario (BC1) are based on metreleptin list price and on a 10 mg vial size, which is currently being considered for marketing authorisation. However, it is expected that vials of 2.5 mg, 5 mg and 10 mg will be approved within three months after marketing authorisation. Therefore, the results of the second base case scenario (BC2) are based on metreleptin list price and on all available vial sizes. The results of the third and fourth base case scenarios (BC3 and BC4) are obtained from BC1 and BC2 after applying a [redacted]PAS price discount to metreleptin since the company expects this to be approved by PASLU.

5.4.1 Headline total QALYs and total costs for metreleptin versus standard care

Table 38 summarises the results of the economic analyses conducted for the four base case scenarios described above. Note that only discounted results are presented and that the difference in scenarios is only on the costs side of the analysis.

function based only on age, gender, type of lipodystrophy, and number of organs impaired, and it is questionable whether this is the most plausible survival function and whether other important covariates were missed.

The ERG identified several issues related to the matching methodology. The first issue is about the appropriateness of the company's approach to the use of data to inform the estimates of treatment effectiveness. Moreover, there is a lack of clarity regarding the matching algorithm used by the company. The ERG also had problems with the independent estimation of the organ impairment transition probabilities from the treated and the matched untreated patient datasets. Furthermore, insufficient interpretation of the matching results was provided.

There are also several issues identified by the ERG, which relate to the extrapolation of blood-lab measures (HbA_{1c} and triglycerides) and other attributes not related to organ damage conducted by the company in the model. Furthermore, while metreleptin discontinuation is only applied for organ impairment, the impact of discontinuation is not reflected in other disease attributes, which creates a bias in favour of metreleptin.

The ERG has several vital concerns about the derivation of the utility decrement from the company's DCE. The key issue is that the use of DCE to directly obtain disutility values for heath states is still in its infancy. The most striking unresolved methodological issue relates to the fact that DCE classifies health states far more often below zero than TTO and produces lower average health state values. Moreover, the face validity of the DCE based disutilities is low, given the derived average QoL utility for SoC of 0.03. This implies that the average patient with lipodystrophy not receiving metreleptin values his/her health state as very close to death, which seems highly unlikely. In addition, various major flaws in the design of the DCE and the analysis of the data were identified, hence, the ERG considers the disutility weights presented by the company as speculative. There are also a few issues related to resource use and costs included in the model, which lead to incompleteness of the model.

Finally, the ERG also has concerns about the sensitivity analyses and the validation of the model. Parameters like treatment costs and discount rates were included in the sensitivity analysis, although these parameters are usually not included in a DSA. It was unclear why the PSA results are presented in four different subgroups. The ERG considered the validation of the model to be inadequate and the information provided about the validation to be very vague and not transparent.

Given the level of evidence submitted by the company, it proved impossible for the ERG to give an indication on the cost-effectiveness of metreleptin. The CE model is based on non-reliable evidence and unjustified assumptions. More specifically, the RWD data used to estimate important inputs for the model is not reliable (e.g. twice data updates without being able to track what was been updated and how, vague definitions of organ impairment were applied). Additionally, both the methods used in quantifying the treatment effect and the DCE methodology used were not transparently reported but more importantly not credible.