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Lead team presentation

Metreleptin for treating lipodystrophy

1st Evaluation Committee Meeting

Highly Specialised Technology, 28 June 2018

Background and clinical effectiveness

Lead team: Sotiris Antoniou

Company: Aegerion

Chair: Peter Jackson

Evidence review group: Kleijnen Systematic Reviews Ltd.

NICE team: Orsolya Balogh, Raisa Sidhu, Sheela Upadhyaya

Disease background

Lipodystrophy (LD)

- Lipodystrophy is a rare, heterogeneous group of syndromes characterised by complete or partial loss or absence of subcutaneous adipose tissue
- Without sufficient adipose tissue the hormone leptin can become deficient
  - 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
  - leading to increased morbidity and mortality, as well as impaired quality of life
- Hyperphagia and female reproductive dysfunction also has a significant impact on quality of life
- Appx 200 people with lipodystrophy in England → a proportion 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, 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:
  - 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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Current treatment options

No standard clinical pathway

- No standard clinical pathway and no licensed treatments available
- 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]

[redacted]new patients each year expected to be eligible for metreleptin treatment [redacted]

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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 circulation from adipocytes
Admin & dose	Recommended daily dose 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** 5

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
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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Clinical expert 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 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

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

Type	Technology	Study
Clinical trials	Metreleptin	NIH 991265/20010769 (pivotal, 1 patient from UK) FHA101^ (supportive, expanded access study in the US) ***Pivotal evidence relevant to the decision problem***
Ongoing observational studies		***Used in economic model***
	Metreleptin	NIH Follow-up study (parameters for the metreleptin arm)
	Comparator	GL/PL Natural History study (parameters for the standard of care arm) ERG stated there were no systematic attempts to identify comparator studies and no selection criteria for reported
	Metreleptin	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 Results expected in Q1/Q2 2018, has been running for 10 years

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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 – ERG highlighted these are surrogate outcomes	

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

Differences in baseline characteristics in metreleptin 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)

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

Differences in baseline characteristics of the population in the metreleptin trial 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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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 metreleptin 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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NIH 991265/20010769 study results

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

Source: Table C22 from CS

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)
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)
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

ERG comment: Simha et al (excluded from search) study with female PL patients showed no significant change from 0 to 6 months in HbA1c levels, insulin, fasting glucose

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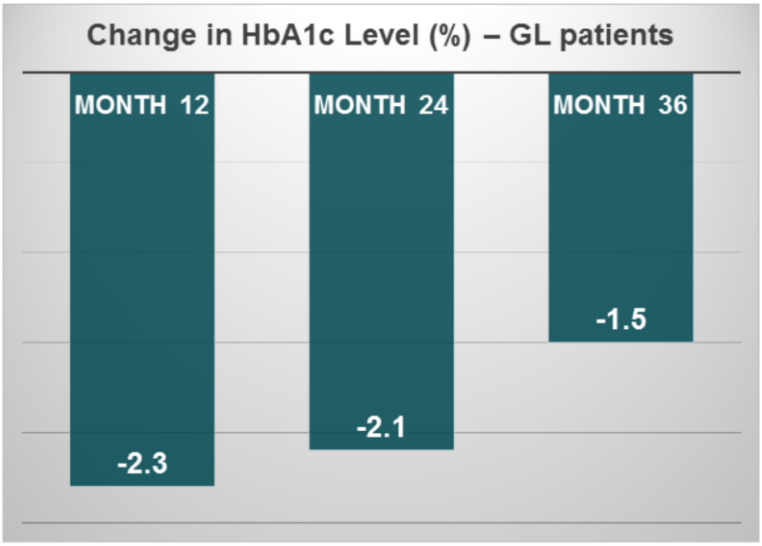
Persistence of metreleptin treatment effects

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



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 submission) 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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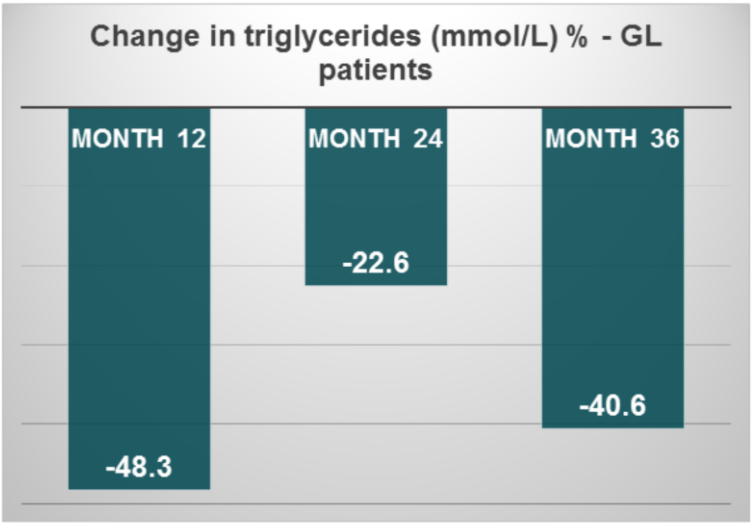
Persistence of metreleptin treatment effects

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



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 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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Clinical results of FHA101 study

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

Source: Table C24 Company submission

Change from baseline in HbA1c (%)		
	GL (N = 9)	PL (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)
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 (N = 9)	PL overall (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)
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**

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

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Clinical results

Other relevant outcomes (1/3)

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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Clinical results

Other relevant outcomes (2/3)

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

Clinical results
Other relevant outcomes (3/3)

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)

Clinical results - Additional ERG comments (1/2)

- The clinical effectiveness section of the CS ***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***

<u>The ERG commented on the above outcomes and provided limited results</u>

➢**Reproductive dysfunction**;

- <u>ERG comment</u>: NIH follow-up study: 21/27 (78%) of relevant female GL, 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

- <u>ERG comment</u>: NIH follow-up study: 95% of effected GL and all effected PL patients experienced improvements in pancreatitis on metreleptin ←→GL/PL natural history study: over the whole observation period 7/56 of GL 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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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 with no evidence of heart abnormalities before metreleptin, 9 (28%) had emergent heart abnormalities after metreleptin initiation -- (6/30 (20%) of PL patients)

- **Measures of health-related quality of life (effects on appearance, 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

- **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, NIH Follow-up study

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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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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Committee, projector and public observer slides - noACIC

Lead team presentation

Metreleptin for treating lipodystrophy

1st Evaluation Committee Meeting

Highly Specialised Technology, 28 June 2018

Presentation from Linn Phipps

Company: Aegerion

Chair: Peter Jackson

Evidence review group: Kleijnen Systematic Reviews Ltd.

NICE team: Orsolya Balogh, Raisa Sidhu, Sheela Upadhyaya

Impact of lipodystrophy

Patient experts

- Lipodystrophy has a wide spectrum of severity and its effects can vary between patients
- Symptoms include:
  - hyperphagia characterised by ever present pursuit of food, resulting in food access issues - significant reduction in the ability to regulate hunger, energy metabolism;
  - metabolic abnormalities including diabetes mellitus;
  - fatigue which has an impact on the daily life;
  - mood and sleeping problems;
  - reproductive dysfunction
- Constraints the rest of people's lives – school, work, social life
- Condition is often overlooked or misdiagnosed
- Patients can need a high level of care (repeated hospital appointments, surgeries and medical interventions); access to treatment might be limited for some people depending on their geographic location
- Burden for carers and wider family can be overwhelming
  - also '*There are worries about risk of suffering or passing the gene to family*'

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Impact of lipodystrophy
Patient perspective

- Major impact on patient's quality of life:

'Ever since I can remember I have had a voracious appetite and was always hungry.'

'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'

'I was diagnosed with alcoholic liver disease … Being diagnosed as an alcoholic when I am teetotal was very distressing.'

'Most patients in this community wait on average 7 years for a correct diagnosis'

'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'

'Self confidence in relationships are very much affected plus on-going fatigue and pain, which is largely unexplored by the medics'

'Living with FPLD is not easy as there are life style changes that need to be made to accommodate it….I don't have an independent life anymore and have had to give up my hobbies and sporting activities'

'…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'

Impact of lipodystrophy on patients

Interviews at the NIH in the US on behalf of company

- The impact of lipodystrophy on the quality of life (QoL) of patients, and their carers/families can be devastating
- Interviews with patients with lipodystrophy were conducted at the NIH in the US on behalf of Aegerion to demonstrate the negative impact of the disease
- Patients (if able) and their carers described the natural history of lipodystrophy, shared their experiences of diagnosis and management of the disease, also the impact of lipodystrophy on their quality of life
  - *"I was bullied really, really bad"*
- They explained that the most devastating symptoms of lipodystrophy are hyperphagia; anxiety; depression; adverse impacts including polycystic ovary syndrome (PCOS), infertility and miscarriage
  - Other symptoms such as fatigue and frequent infection/illness
- These can lead to impaired or complete inability to work or attend school, as well as to social isolation – *'I'm nor able to work'*
- Female patients can experience reproductive problems: *'My menstrual periods were out of control'*

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Impact of lipodystrophy on carers

Interviews at the NIH in the US on behalf of company

- Patients had often experienced symptoms at a young age
  - Carers may need to provide 24/7 supervision
- Hyperphagia can lead to disruptive activity in young children, which can be socially isolating for their carers
- The extreme level of food seeking additionally creates stress on families/carers
- '*Just at 3 years old I've just now allowed her to start playing with food and play food and play utensils and things like that, I never permitted her to play with them because everything was associated as food so even the play food, she ate it and I don't mean bit, I mean she ate it, she took bites and she swallowed*'
- Experience of pregnancy loss and infertility can have a considerable impact on partners

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Benefits of metreleptin
Patient perspective

- Metreleptin is the only treatment for lipodystrophy, and according to the patients, it has a positive impact on metabolic profile, satiety levels, everyday life

'Leptin reduces appetite, which is huge social and health problem'

'*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….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%....The fat on my liver has dropped by almost 75%...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*'

'*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*'

'*Leptin has appeared to stabilise and prevent further liver damage*'

Slides for projector and public - noACIC

Lead team presentation

Metreleptin for treating lipodystrophy

1st Evaluation Committee Meeting

Highly Specialised Technology, 28 June 2018

Economic effectiveness

Lead team: Carrie Gardner

Company: Aegerion

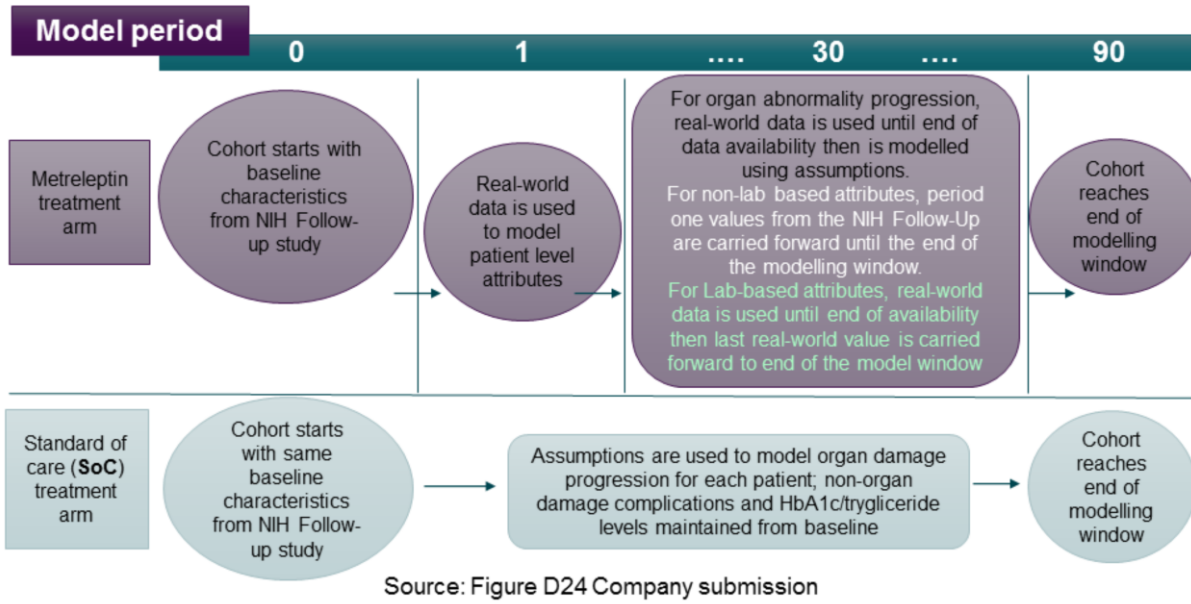
Chair: Peter Jackson

Evidence review group: Kleijnen Systematic Reviews Ltd.

NICE team: Orsolya Balogh, Raisa Sidhu, Sheela Upadhyaya

Company modelling approach

Individual patient level modelling; 1 year cycles 90 year time horizon



Source: Figure D24 Company submission

- Model evaluates health states of individual patients defined through a set of 13 total attributes obtained from the NIH Follow-up study → these attributes determine a patient's QALY value in each period

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Evidence sources and assumptions (1/2)

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

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

ERG comments

Model

- 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 final list of attributes included in model were selected
    - unclear whether any other relevant and important attributes for lipodystrophy patients were not included
  - 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)

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 (organs damaged)	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 applied to patients from baseline until the end of time horizon

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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 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 and inherent structural censoring
  - *Patients observed from enrolment in the NIH Follow-up trial ←→ in the GL/PL study, retrospective patient records 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 and from the GL/PL studies
  - *Not clear whether a death event considered as a censor or an organ impairment event (categorisation of death has an 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 → ***removed in exploratory scenario analyses by ERG***

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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 algorithm, for each patient died/ censored in the GL/PL study; pseudo patients that died/censored patient were created
- Insufficient interpretation of the matching results
  - Size of untreated matched dataset (N=47) is approximately 1/3 of the treated patients' dataset (N=112) → an untreated patient is matched to multiple treated patients from the NIH Follow-up study → clinical inputs used not trustworthy

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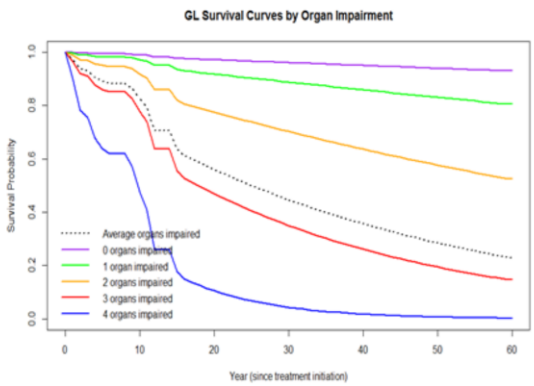
Derivation of mortality inputs for the model

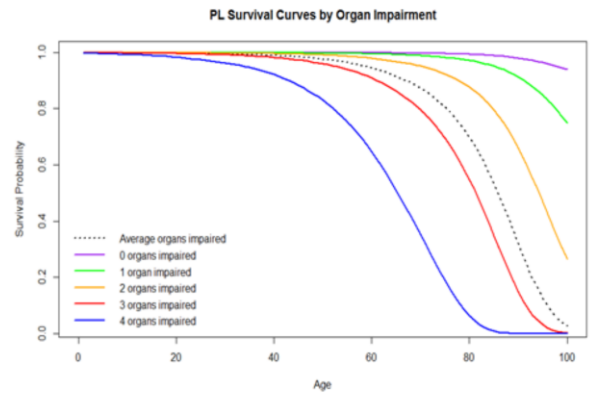
Extrapolation of the survival

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 of organ impairment, length of time have no impact)





Source: Company submission Figure 40 and 41

ERG comments on mortality

- Cox proportional hazards model is used to estimate the relationship between organ abnormality and mortality (ERG: Cox PH model is fit on the natural history study data)
  - Extrapolation was conducted on patients from the *NIH follow-up study* ←→ estimation exercise was conducted on patients from the *GL/PL natural history study*
  - Hazard ratio from estimation applied to the parametric/life table survival curves obtained from extrapolation
    - *ERG stated the same data sets should have been used* for consistency
- 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)
  - Company used updated model with annual survival probability from UK life table if the survival probability estimates based on NIH Follow-up and GL/PL natural history studies were more favourable
    - *ERG highlighted this is an artificial solution, instead reasons underlying the high survival outcomes from the model should have been explored*
- 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
  - *Baseline survival curves do not represent a patient population in whom number of organ impairments stayed fixed → scaling these to conditional survival curves overestimated the difference in survival at later time points*

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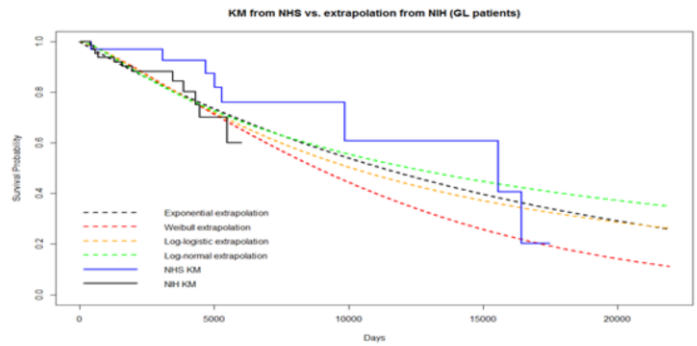
Further ERG comments on mortality

To check clinical plausibility of the GL survival extrapolation – ERG asked the company to provide external data or expert opinion

- 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



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

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 therefore 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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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*
    - E.g. DCE classifies health states below zero more often than time trade-off and produces lower average health state values
- 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 attributes that the company mentioned as having impact on the patient's QoL, but 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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ERG comments
HRQoL (2/2)

- The ERG highlighted concerns around the face validity of DCE based disutilities
  - Number of QALYs was relatively low, especially in the SoC arm
    - 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: 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*

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** 47

Base-cases considered in the economic analyses

- 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; the PAS will apply to all vial sizes once available

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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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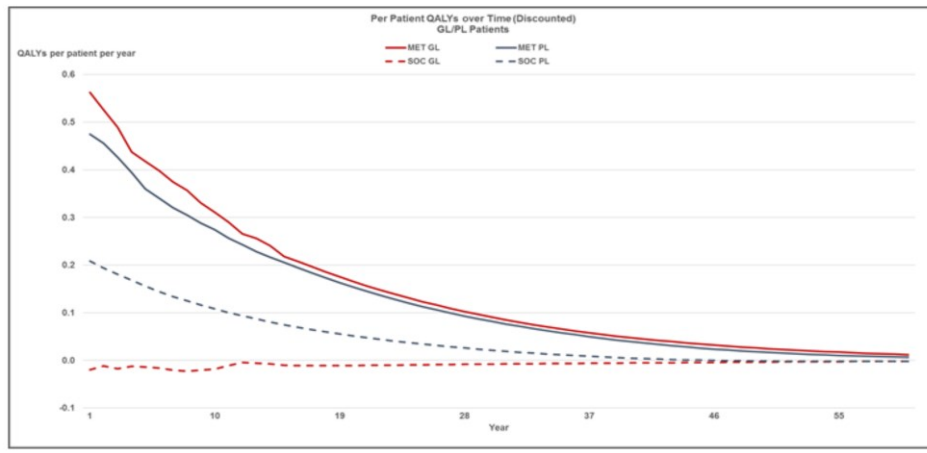
QALY gains with metreleptin treatment

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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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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ERG corrected company base case scenarios (discounted)

Marginal impact on results

- Company provided 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 → ERG undid most of the changes
- ERG identified two additional errors in the model: ***1)*** Wrong transition probability used for the 4th 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

	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

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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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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

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

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?