NICE National Institute for Health and Care Excellence

HIGHLY SPECIALISED TECHNOLOGIES

Metreleptin for treating lipodystrophy [ID861] HST reconsideration

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Metreleptin for treating lipodystrophy [ID861]
HST reconsideration

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission (reconsideration)** from Amryt Pharma
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Diabetes UK
   b. Lipodystrophy UK & submission appendix
   c. National Severe Insulin Resistance Service, Addenbrooke's Hospital
4. **Expert personal perspectives** from:
   a. Prof T Tan, – clinical expert, nominated by Diabetes UK
5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews
6. **Evidence Review Group report – factual accuracy check**
7. **Technical report**
8. **Technical engagement response from Amryt Pharma**
9. **Technical engagement questions and responses from experts:**
   a. Prof T Tan, – clinical expert, nominated by Diabetes UK
   b. Prof S O'Rahilly – clinical expert, nominated by Amryt Pharma
   c. Dr A Stears – clinical expert, nominated by Amryt Pharma
10. **Technical engagement responses from consultees and commentators:**
    a. Lipodystrophy UK
11. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews
12. **Company additional information**

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Metreleptin for treating lipodystrophy [ID861]

Re-submission

May 2020

Contents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 1
Highly Specialised Technologies Evaluation Programme 1
Contents 2
List of figures 4
List of tables 7
Glossary of terms 11
Executive Summary 15
Section A – Decision problem 24
1 Statement of the decision problem 24
2 Description of technology under assessment 29
3 Regulatory information 31
4 Ongoing studies 32
5 Equality 34
Section B – Nature of the condition 35
6 Disease morbidity 35
7 Impact of the disease on quality of life 48
8 Extent and nature of current treatment options 65
Section C – Impact of the new technology 76
9 Published and unpublished clinical evidence 76
10 Measurement and valuation of health effects 150
11 Existing economic studies 165
12 Economic analysis 166
13 Cost to the NHS and Personal Social Services 225
Section E – Impact of the technology beyond direct health benefits 232
14 Impact of the technology beyond direct health benefits 232
Section F - Managed Access Arrangements 237
15 Managed Access Arrangement 237
16 References 238
17 Appendices 255
17.1 Appendix 1: Search strategy for clinical evidence 255
17.2 Appendix 2: Search strategy for adverse events 274
17.3 Appendix 3: Search strategy for economic evidence 275
17.4 Appendix 4: Resource identification, measurement and valuation 281
17.5 Appendix 5: Search strategy for HRQL evidence 284

17.6 Appendix 6: List of studies 287
17.7 Appendix 7: Addenbrooke's Hospital early-access data: Organ Damage and Complications at Baseline 304
17.8 Appendix 8: Critical appraisals of study NIH studies 991265/20010769 and FHA101 using the Downs and Black checklist 306
17.9 Appendix 9: NIH studies 991265/200110769 – further exploratory analyses 312
17.10 Appendix 10: FHA101 expanded access study: supportive evidence ...315
17.11 Appendix 11: Pooled safety analysis 320
17.12 Appendix 12: Indirect treatment comparison.....321
17.13 Appendix 13: Cost effectiveness model 370

List of figures

Figure 1: Consequences of adipose tissue loss 41
Figure 2: Clinical consequences associated with leptin-deficient lipodystrophy 42
Figure 3: Selected quotes in lipodystrophy patients and carers: Anxiety and depression 49
Figure 4: Selected quoted in lipodystrophy patients and carers: reproductive dysfunction 52
Figure 5: Selected quoted in lipodystrophy patients and carers: compromised immune system 53
Figure 6: Selected quotes in lipodystrophy patients and carers: fatigue (55) 54
Figure 7: Selected quotes in lipodystrophy carers: changes to responsibilities 55
Figure 8: Effect of metreleptin on a young girl (age 23 months old) with regard to A) acanthosis nigricans and B) hepatic steatosis 62
Figure 9: A guide to diagnosing different subtypes of lipodystrophy 69
Figure 10: Schematic for the clinical SLR 79
Figure 11: Study design for studies (a) NIH 991265 and (b) NIH 20010769 84
Figure 12: Study design for FHA101 88
Figure 13: Mean change in HbA1c (%) and triglycerides (mmol/L) from baseline at month 12/LOCF in patients with GL treated with metreleptin in NIH studies 991265/20010769 106
Figure 14: Mean change in HbA1c (%) and triglycerides (mmol/L) from baseline at month 12/LOCF in patients with PL treated with metreleptin in NIH studies 991265/20010769 109
Figure 15: Mean (SEM) change in HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24, 36 and 48 of metreleptin treatment in NIH studies 991265/20010769 in GL patients 111
Figure 16: Mean (SEM) HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24 and 36 of metreleptin treatment (FAS population) in NIH studies 991265/20010769 in PL subgroup patients 112
Figure 17: Study design of the GL/PL Natural History Study 129
Figure 18: NICE DSU TSD 17 algorithm used for method selection (Figure 1) (18) 133
Figure 19: Continued NICE DSU TSD 17 algorithm used for method selection (Figure 2) (18): 134
Figure 20: Continued NICE DSU TSD 17 algorithm used for method selection (Figure 3): . 134
Figure 21: Histogram illustrating distribution of age across the GL/PL Natural History study and the NIH Follow-up study 136
Figure 22: Schematic for the economic, cost and resource use, and HRQL SLR 154
Figure 23: Individual patient-level model structure 168
Figure 24: Pancreatitis sub-model structure 169
Figure 25: Liver sub-model structure 170
Figure 26: Cardiovascular sub-model structure 171
Figure 27: Kidney sub-model structure 172
Figure 28: Neuropathy sub-model structure 173
Figure 29: Retinopathy sub-model structure 174
Figure 30: OWSA ICER results 215
Figure 31: Probabilistic sensitivity analysis scatterplot 216
Figure 32: Cost-effectiveness acceptability curve 217
Figure 33: Survival of GL, female patients 220
Figure 34: Survival of GL, male patients 221
Figure 35: Survival of PL, female patients 221
Figure 36: Survival of PL, male patients 222

Figure 37: Previous submission PRSIMA diagram to show the identification of economic evaluations associated with lipodystrophy 280
Figure 38: Previous submission PRISMA diagram to show the identification of HRQL associated with lipodystrophy 286
Figure 39: Histogram illustrating distribution of HbA1c change 327
Figure 40: Histogram illustrating distribution of triglyceride change 328
Figure 41: Histogram illustrating distribution of ALT change 329
Figure 42: Histogram illustrating distribution of AST change 330
Figure 43: Boxplot showing naive comparison of change in HbA1c of metreleptin with or without supportive care compared to standard of care (supportive care) at Month 12 compared to baseline 332
Figure 44: Boxplot showing naive comparison of change in triglycerides of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline ... 335
Figure 45: Boxplot showing naive comparison of change in ALT of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline 337
Figure 46: Boxplot showing naive comparison of change in AST of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline 339
Figure 47: Naïve Kaplan-Meier curve of metreleptin with or without supportive care and supportive care 342
Figure 48: Q-Q plot assessing the normality of residuals from HbA1c multivariate regression 343
Figure 49: Q-Q plot assessing the normality of residuals from triglycerides multivariate regression 344
Figure 50: Q-Q plot assessing the normality of residuals from ALT multivariate regression 345
Figure 51: Q-Q plot assessing the normality of residuals from AST multivariate regression 346
Figure 52: Lipodystrophy type distribution before and after IPW in HbA1c outcome using stabilized weights 350
Figure 53: Distribution of age before and after IPW in HbA1c outcome using stabilized weights 350
Figure 54: Distribution of gender before and after IPW in HbA1c outcome using stabilized weights 350
Figure 55: Distribution of age before and after IPW in triglyceride outcome outcome using stabilized weights 353
Figure 56: Lipodystrophy type distribution before and after IPW in triglyceride outcome 353
Figure 57: Distribution of gender before and after IPW in triglyceride outcome 353
Figure 58: Distribution of age before and after IPW in ALT outcome 356
Figure 59: Lipodystrophy type distribution before and after IPW in ALT outcome 356
Figure 60: Distribution of gender before and after IPW in ALT outcome 356
Figure 61: Distribution of age before and after IPW in AST outcome 359
Figure 62: Lipodystrophy type distribution before and after IPW in AST outcome 359
Figure 63: Distribution of gender before and after IPW in AST outcome 359
Figure 64: Lipodystrophy type distribution before and after IPW in pancreatitis outcome 362
Figure 65: Distribution of age before and after IPW in pancreatitis outcome 362
Figure 66: Distribution of gender before and after IPW in pancreatitis outcome 362
Figure 67: Distribution of age before and after IPW in imputed pancreatitis outcome 365
Figure 68: Lipodystrophy type distribution before and after IPW in imputed pancreatitis outcome 365
Figure 69: Distribution of gender before and after IPW in pancreatitis outcome 365
Figure 70 :Lipodystrophy type distribution before and after IPW in mortality outcome 368
Figure 71: Distribution of age before and after IPW in mortality outcome 368

Figure 72: Distribution of gender before and after IPW in mortality outcome 368

List of tables

Table 1: Statement of the decision problem 25
Table 2: Dosing Information of technology being evaluated (21) 29
Table 3: Ongoing studies relevant to the decision problem 32
Table 4: Essential Features of Generalised Lipodystrophy 37
Table 5: Essential Features of Partial Lipodystrophy 39
Table 6: Mortality events by contributing factors 47
Table 7: Illustrations of impaired physical appearance in lipodystrophy 50
Table 8: Range of complications and impact on QoL associated with lipodystrophy 57
Table 9: Overview of the NHS service specification for patients with lipodystrophy 66
Table 10: Additional Treatments for specific comorbidities 71
Table 11: Key changes in the de novo clinical SLR approach taken to address previous concerns raised by NICE and / or the ERF 76
Table 12: List of relevant published studies 82
Table 13: List of relevant unpublished studies 82
Table 14: Summary of methodology for NIH studies 991265/200110769 85
Table 15: Summary of methodology for study FHA101 88
Table 16: Baseline characteristics for NIH studies 991265/200110769 92
Table 17: Baseline characteristics for study FHA101 94
Table 18: Baseline characteristics for Early Access Programme data Addenbrooke's Hospital 98
Table 19: Patient disposition in NIH studies 991265/200110769 100
Table 20: Patient disposition in study FHA101 101
Table 21: Outcomes from NIH studies 991265/20010769 102
Table 22: Change from baseline to Month 12/LOCF in HbA1c and fasting triglycerides using LOCF for patient subgroups (FAS Population) 115
Table 23: Results from Early Access Programme at Addenbrooke's Hospital 120
Table 24: Adverse events: NIH studies 991265/20010769 (safety analysis set) 123
Table 25: Patient Demographic and Clinical Characteristics in the GL/PL Natural History Study 131
Table 26: Missingness and appropriateness for imputation in NIH Follow-up study and GL/PL Natural History study 138
Table 27: Stabilised inverse probability weighting results showing ATE of metreleptin with or without supportive care compared to supportive care alone in HbA1c change from baseline to Month 12 142
Table 28: Inverse probability weighting results showing ATE of metreleptin with or without supportive care compared to supportive care alone in triglyceride change from baseline to Month 12 142
Table 29: Inverse probability weighting results showing ATE of metreleptin with or without supportive care compared to supportive care alone in ALT change from baseline to Month 12 143
Table 30: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in AST change from baseline to Month 12 143
Table 31: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in incidence of pancreatitis 144
Table 32: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in incidence of pancreatitis (imputed) 144

Table 33: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in all-cause mortality 145
Table 34: Summary of HRQL study details 156
Table 35: Summary of quality-of-life values for cost-effectiveness analysis 159
Table 36: Baseline characteristics, patients with GL and PL 167
Table 37: Baseline characteristic inputs from the NIH studies 991265/20010769 (27,80) ... 175
Table 38: Model assumptions 177
Table 39: Key features of model not previously reported 181
Table 40: Probability of different cardiovascular events 182
Table 41: Clinical data used to drive transitions in each of the sub-models 183
Table 42: Clinical transition probabilities 190
Table 43: Summary of variables applied in cost-effectiveness model 193
Table 44: Summary of the number of EAP patients currently receiving each metreleptin vial size 197
Table 45: Costs per outpatient appointment for routine monitoring of patients with lipodystrophy 198
Table 46: Total routine monitoring costs for patients with lipodystrophy in year 1 and year 2 onwards 198
Table 47: Expected medication reductions for patients with PL 200
Table 48: Expected medication reductions for patients with GL 200
Table 49: Drug costs for supportive care 201
Table 50: Scenario analysis 207
Table 51: Base-case results - discounted 211
Table 52: Undiscounted base-case results 213
Table 53: Scenario analysis results 215
Table 54: Estimated eligible patient numbers for metreleptin 226
Table 55: Expected uptake rate of metreleptin over the next 5 years 227
Table 56: Summary of the number of EAP patients currently receiving each vial size 228
Table 57: Overall lipodystrophy (GL and PL) budget impact analysis – scenario with all vial sizes available (PAS price) 229
Table 58: EMBASE, Medline, Medline® In-Process search strategy (EMBASE interface) .. 256
Table 59: Clinical search strategy - Cochrane Central Register of Controlled Trials (Cochrane Library interface) 260
Table 60 - Inclusion and exclusions criteria for published and unpublished studies 261
Table 61: Summary of previous SLR references with reasons for exclusion 264
Table 62: Second Pass References Excluded 268
Table 63: Economic evidence search strategy 275
Table 64: Economic evidence search strategy - Cochrane Central Register of Controlled Trials (Cochrane Library interface) 277
Table 65: The inclusion and exclusion criteria for economic evidence 279
Table 66: Inclusion and exclusion criteria for resource identification, valuation and measurement studies 281
Table 67: Selection criteria used for published HRQL studies 284
Table 68: Metreleptin Study Results: NCT01679197 288
Table 69: Metreleptin Study Results: NCT00025883 288
Table 70: Metreleptin Study Results: NCT01778556 290
Table 71: Metreleptin Study Results: NCT00005905 290
Table 72: Metreleptin Study Results: NCT02262806 291

Table 73: Metreleptin Study Results: NCT02262832 292
Table 74: Metreleptin Study Results: NCT00677313 292
Table 75: Metreleptin Study Results: NCT00001987 292
Table 76: Metreleptin Study Results: NCT00457938 293
Table 77: Metreleptin Study Results: NIH991265 293
Table 78: Metreleptin Study Results: NIH20010796 293
Table 79: Metreleptin Study Results: RO1 DK88114 294
Table 80: Metreleptin Study Results: Others 294
Table 81: Non-Metreleptin Study Results: USA 297
Table 82: Non-Metreleptin Study Results: Brazil 298
Table 83: Non-Metreleptin Study Results: Turkey 299
Table 84: Non-Metreleptin Study Results: Other/Not Reported 300
Table 85: Unpublished Study Results 303
Table 86: Organ Damages and Complications at Baseline from Addenbrooke's Hospital early-access program data 304
Table 87: Critical appraisal of study NIH studies 991265/20010769 306
Table 88: Critical appraisal of study FHA101 309
Table 89: Primary Efficacy Endpoints: Change from Baseline to Month 12 in HbA1c and Fasting Triglycerides using LOCF (CFAS Population) 313
Table 90: Outcomes from Study FHA101 315
Table 91: Adverse events: Study FHA101 (safety analysis set) 318
Table 92: 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) 320
Table 93: Naïve analysis of mean HbA1c change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline 332
Table 94: Naïve analysis of mean triglyceride change of metreleptin with or without supportive care compared to standard of care (supportive care) at Month 12 compared to baseline.... 334
Table 95: Naïve analysis of mean ALT change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline 336
Table 96: Naïve analysis of mean AST change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline 338
Table 97: Naïve analysis of pancreatitis presence post-treatment of metreleptin with or without supportive care compared to supportive care (complete case analysis). 340
Table 98: Naïve analysis of pancreatitis presence post-treatment of metreleptin with or without supportive care compared to supportive care (complete case analysis). 340
Table 99: Naïve analysis of mortality post-baseline of metreleptin compared to supportive care 341
Table 100: Linear regression of change in HbA1c against study type, age, gender and lipodystrophy type. 343
Table 101: Linear regression of change in triglycerides against study type, age, gender and lipodystrophy type. 344
Table 102: Linear regression of change in ALT against study type, age, gender and lipodystrophy type 346
Table 103: Linear regression of change in AST against study type, age, gender and lipodystrophy type 347
Table 104: General linear model of incidence of pancreatitis at outcome timepoint against study type, age, gender and lipodystrophy type 347
Table 105: General linear model of incidence of pancreatitis (imputed in supportive care study) at outcome timepoint against study type, age, gender and lipodystrophy type 348

Table 106: Cox regression model assessing mortality against study type, age, gender and lipodystrophy type 348
Table 107: A summary of patient characteristics before and after weighting in HbA1c change from baseline to Month 12 349
Table 108: Statistical summary of covariate balance before and after IPW with stabilized weights in HbA1c outcome 351
Table 109: A summary of patient characteristics before and after weighting in triglyceride change from baseline to Month 12 352
Table 110: Statistical summary of covariate balance before and after IPW in triglyceride outcome 354
Table 111: A summary of patient characteristics before and after weighting in ALT change from baseline to Month 12 355
Table 112: Statistical summary of covariate balance before and after IPW in ALT outcome 357
Table 113: A summary of patient characteristics before and after weighting in AST change from baseline to Month 12 358
Table 114: Statistical summary of covariate balance before and after IPW in AST outcome 360
Table 115: A summary of patient characteristics before and after weighting in incidence of pancreatitis 361
Table 116: Statistical summary of covariate balance before and after IPW in pancreatitis outcome 363
Table 117: A summary of patient characteristics before and after weighting in incidence of pancreatitis (with imputation) 364
Table 118: Statistical summary of covariate balance before and after IPW in pancreatitis outcome 366
Table 119: A summary of patient characteristics before and after weighting in all-cause mortality 367
Table 120: Statistical summary of covariate balance before and after IPW in mortality outcome 369
Table 121: Baseline medication by class 370
Table 122: Baseline medication as determined by prescription cost data 2018 370
Table 123: Insulin cost per unit 371
Table 124: Weighted average cost per unit of insulin 371
Table 125: Dose-dependent daily medication cost 371
Table 126: Baseline daily medication cost for study cohort 372
Table 127: Baseline medication costs per patient 372
Table 128: Proportion of patients able to stop medication 372
Table 129: Proportion of patients able to reduce medication 373
Table 130: Daily cost per medication for patients able to reduce dose 373
Table 131: Expected post-metreleptin daily medication costs for study cohort 373
Table 132: Expected post-metreleptin medication costs per patient 374
Table 133: Variables used in One-way sensitivity analysis 375
Table 134: Variables used in probabilistic sensitivity analysis 380

Glossary of terms

Term	Definition
AACE	American Association of Clinical Endocrinologists
ACC	Acetyl-CoA carboxylase
ADRA2A	Adrenoceptor alpha 2A
AE	Adverse event
AGL	Acquired generalised lipodystrophy
AGPAT2	1-acylglycerol-3-phosphate O-acyltransferase 2
ALT	Alanine aminotransferase
AMPK	Adenosine monophosphate-activated protein kinase
APL	Acquired partial lipodystrophy
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATE	Average treatment effect
BID	Twice daily
BMI	Body mass index
BSCL2	Berardinelli-Seip type 2
BSS	Berardinelli-Seip Syndrome
CAV1	Caveolin 1
CCG	Clinical commissioning group
CEAC	Cost-effectiveness acceptability curve
CGL	Congenital generalised lipodystrophy
CI	Confidence interval
CIDEC	Cell-death-inducing DNA
CSR	Clinical study report
CUH	Cambridge University Hospitals
D	Day
DCCT	Diabetes Control and Complications Trial
DCE	Discrete choice experiment
DSU	Decision Support Unit
EAP	Early Access Programme
ECLip	European Consortium of Lipodystrophies

EDIC	Epidemiology of Diabetes Interventions and Complications
EMA	European Medicines Agency
EQ-5D	EuroQoL 5-dimensions
ERG	Evidence review group
ESRD	End-stage renal disease
FAS	Full analysis set
FDA	Food and Drug Administration
FFA	Free fatty acid
FPL	Familial partial lipodystrophy
FPLD	Familial partial lipodystrophy disease
GL	Generalised lipodystrophy
GP	General practitioner
HbA1c	Haemoglobin A1C
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IGF	Insulin-like growth factor
IPW	Inverse probability weighting
IRS	Insulin receptor substrate
JAK	Janus Kinase
LDL-C	Low density lipoprotein cholesterol
LIPE	Hormone-sensitive lipase
LOCF	Last observation carried forward
LS mean	Least-squares mean
M	Month
MAA	Marketing authorisation application
MAPK	Mitogen-activated protein kinase
MCS	Mental Component Summary
MMRM	Mixed-effect model repeated measures
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NNH	Number needed to harm
NNT	Number needed to treat
OWSA	One-way sensitivity analysis
PCOS	Polycystic ovary syndrome
PCS	Physical Component Summary
PI3K	Phosphatidylinositol 3 kinase
PL	Partial lipodystrophy
PLIN1	Perilipin 1
PPARG	Peroxisome proliferator activated receptor gamma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
PS	Propensity score
PSA	Probabilistic sensitivity analysis
PTRF	Polymerase I and transcript release factor
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
Rh	Recombinant human
SAE	Serious adverse event
SC	Supportive care
SD	Standard deviation
SEM	Standard error of the mean
SLR	Systematic literature review
SoC	Standard of Care
STAT	Signal transducer and activator of transcription
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TSD	Technical Support Document
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
ULN	Upper limit of normal
US	United States

W	Week
WTP	Willingness-to-pay
ZBI	Zarit Caregiver Burden Interview

Executive Summary

This re-submission seeks to address concerns raised by NICE on the clinical and cost-effectiveness of metreleptin, summarised in the Final Evaluation Document (FED) - June 2019 (now withdrawn) (1) and the letter from NICE confirming the reconsideration step dated 2nd August 2019.

Amyrt Pharmaceuticals DAC acquired Aegerion in September 2019 and has prepared this re-submission. We have worked extensively and in collaboration with the European Consortium of Lipodystrophies (ECLip), selected clinical experts in a Delphi Panel and lipodystrophy specialists from Addenbrooke's Hospital, the leading National Health Service (NHS) centre managing lipodystrophy patients in England, to improve the evidence base for metreleptin and to address the concerns arising from the previous submission. This has included:

- Updating and strengthening clinical and economic literature reviews to ensure they are optimal
- Conducting a robust *de novo* indirect treatment comparison (ITC) aligned with the Decision Support Unit's preferred methodology
- Gathering further evidence on the impact of the disease on caregivers of lipodystrophy patients, principally through the implementation of a survey.
- Building a *de novo* economic model that reflects disease progression, leveraging metabolic modelling methods and comparatively larger and more established underlying evidence base within diabetes and other relevant conditions as well as the Delphi Panel and *UK Lipodystrophy Patient and Caregiver Survey*.

We feel this comprehensive approach addresses the issues and concerns raised in the initial submission. Furthermore, we have also discussed and sought input on our approach with the NICE Highly Specialised Technologies (HST) team, and we look forward to continuing to work together with them as

well as the HST Committee and the evidence review group (ERG) in the coming months.

Nature of the condition

Lipodystrophy comprises a clinically heterogeneous group of congenital or acquired disorders associated with complete (generalised lipodystrophy [GL]) or partial loss of adipose tissue (partial lipodystrophy [PL]) (2). It is a progressive, chronic and life-threatening disease that affects multiple organs resulting in significant morbidity and premature mortality.

The heterogeneity of lipodystrophy means its impact varies from patient to patient, but it can frequently be extensive and severe, leading to a huge detrimental impact on patients, reducing life expectancy and quality of life, and the inability to carry out even basic daily activities. This impact is also felt by the carers and family members of lipodystrophy patients.

The pathogenesis and the severity of lipodystrophy is mediated by the irreversible loss of subcutaneous adipose tissue, leading to a reduced capacity to store excess calories and a deficiency of the hormone leptin – an important regulator of energy homeostasis and fat and glucose metabolism, and the key satiety signal for the brain. Patients' ability to regulate their energy and hunger and metabolise glucose and fat is thus impaired (3–5), resulting in ectopic fat deposition, and in turn insulin-resistant diabetes (haemoglobin A1c [HbA1c] level >6.5%) and hypertriglyceridaemia (triglyceride level >200 mg/dL or 2.26mmol/L). This combination of conditions is extremely challenging to manage with current supportive care comprising of lipid-lowering and anti-hyperglycaemic therapies (2,5–7).

These metabolic disorders, together with ectopic fat deposition in various organs and the musculature, cause a multifaceted and complex network of conditions and comorbidities including severe cardiovascular complications and potentially irreversible damage to the organs including the liver (hepatic steatosis, cirrhosis, hepatocellular carcinoma, liver failure), kidneys (nephropathy, proteinuria, renal failure) and pancreas (acute pancreatitis).

In addition to the physical impact (8), lipodystrophy patients are further encumbered by an increased prevalence of psychological and psychiatric conditions including anxiety, depression and eating disorders (9) – exacerbating their already high risk of severe morbidity, impaired quality of life and premature death (2,10,11).

Patients often require extensive and long-term support from multiple carers, who suffer themselves due to the impact of disease. Many carers experience anxieties, depression and deteriorating mental health, often acquiring and/or neglecting their own physical and mental health conditions, feeling the needs of the patients they care for come before their own. Their responsibilities also impair their day-to-day activities and ability to work, ultimately leading to social isolation and loss of earning amongst other detrimental effects (12).

Lipodystrophy is currently primarily managed through diet and lifestyle modification. Symptomatic treatment regimens such as lipid-lowering and anti-hyperglycaemic therapies (including maximised conventional therapies for hypertriglyceridaemia, such as fibrates and fish oils) attempt to mitigate hyperglycaemia and hypertriglyceridaemia, and through this prevent downstream complications. However, many patients are refractory to these, leading to inadequate and ineffective diabetes control despite the use of combinations of therapies including extremely high, clinically impractical insulin doses far beyond those used in conventional diabetes management (13). With no other effective treatment available, patients are effectively unguarded from the high risk of complications in multiple organs, extreme physical and mental anguish, and premature mortality (14–16).

Impact of the new technology

Leptin replacement therapy with metreleptin (brand name: Myalepta®), an analogue of the human hormone leptin, is the first and only licensed treatment targeting the underlying cause of GL and PL, which is leptin deficiency. Metreleptin acts centrally to decrease glucose, triglyceride and other lipid intermediates, reducing their ectopic accumulation in tissues and organs, and ameliorating severe insulin resistance and organ damage. This restores

patients' metabolic function, slowing, halting or even (in some cases) reversing disease progression and organ damage, and thus carrying the potential to greatly improve patients' quality of life and survival.

Marketing authorisation was granted on the 29th July 2018 by the European Medicines Agency (EMA): metreleptin is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy patients with:

- Confirmed congenital GL (Berardinelli-Seip syndrome) or acquired GL (Lawrence syndrome) in adults and children 2 years of age and above
- Confirmed familial PL or acquired PL (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom supportive care treatments have failed to achieve adequate metabolic control.

The clinical effectiveness of metreleptin in lipodystrophy patients has been demonstrated, primarily through the pivotal open-label, single-arm National Institutes of Health (NIH) studies 991265/200110769 (17). The NIH follow up study (an extension of the NIH studies 991265/20010769) retrospectively collected further long-term data and additional outcomes, including the comparison of patient-relevant outcomes pre- and post-treatment, from patients in the NIH studies 991265/20010769 who received metreleptin via a chart review (16). Of note, these studies covered by far the largest group of lipodystrophy patients ever investigated and provided long-term data (up to 14 years) on these patients.

To generate additional clinical effectiveness estimates in comparison with supportive care, a *de novo* ITC compared the NIH follow-up study (16) to the most relevant comparator study – the GL/PL Natural history study (an observational study for GL and PL patients receiving supportive care) (15) using methods outlined in NICE Decision Support Unit Technical Support Document (TSD) 17 (18). This analysis demonstrated statistically significant and highly clinically meaningful benefits for metreleptin for HbA1c, triglycerides, liver transaminases (aspartate aminotransferase (AST), alanine aminotransferase

(ALT)) as an indicator for liver damage, and episodes of pancreatitis for lipodystrophy patients. The adjusted HbA1c results from the ITC were consistent with the observed results in the NIH 991265-20010769 studies, demonstrating that these were representative of comparative effectiveness estimates compared to supportive care.

In the NIH study, a clinically meaningful and highly significant decrease in HbA1c, triglyceride level, and liver volume with metreleptin was demonstrated (17,19,20). Between baseline and month 12/last observation carried forward (LOCF), the mean absolute change in HbA1c was -2.2% in GL patients ($p<0.001$) and -0.9% ($p<0.001$) in the PL subgroup (patients with HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L at baseline), and the mean relative change in triglycerides from baseline to Month 12/LOCF was -32.1% ($p=0.001$) in the GL group and -37.4% ($p<0.001$) in the PL subgroup excluding the one outlying noncompliant patient (17,19,20). Furthermore, at baseline, 31% (21 of 68) of GL patients and 52% (23 of 44) of PL patients had ≥1 episode of pancreatitis in the year prior to metreleptin initiation, and in the NIH follow up study, a dramatic reduction in episodes of pancreatitis occurred in 95% (20 of 21) of GL patients and in 100% (23 of 23) of PL patients comparing events before treatment with metreleptin and post-metreleptin (16).

A consistent clinical benefit versus supportive care was demonstrated in the ITC. In GL and PL patients combined, the analysis demonstrated a -1.52% absolute change in HbA1c ($p<0.001$), an estimated 915 mg/dL (10.34 mmol/L) reduction in triglycerides ($p<0.001$), and a 6% reduction in the odds of an episode of pancreatitis (corresponding to an odds ratio of 0.94; $p=0.01$) with metreleptin compared to supportive care alone from baseline to month 12.

Long term results from NIH studies 991265/20010769 up to 48 months in GL patients and 36 months in the PL patient subgroup showed sustained clinically meaningful improvements in HbA1c and triglyceride levels. Evidence from Addenbrooke's Hospital Early Access Programme (EAP) further supports this, with sustained improvements in glycaemic control and hypertriglyceridaemia observed in both GL and PL patients up to 36 months.

The EMA concluded metreleptin to have an acceptable overall safety profile (21); drug-related serious adverse events were not common and were consistent with the underlying lipodystrophy.

The results from the metreleptin pivotal clinical trials were confirmed by real world evidence from the EAP running for more than 10 years in Addenbrooke's Hospital (in addition to several other European centres). Under the EAP, several patients are responding well to metreleptin, which has provided effective management of their lipodystrophy. Continued access is crucial to these patients and their families. As such, Addenbrookes reviewed their current data collection and have set up an enhanced data collection for patients receiving metreleptin from the anticipated date of NICE issuing a positive recommendation for the use of metreleptin (January 2021) (22). This data collection will be part of the clinical care pathway and will be made available to NHS England on a regular basis; EClip and its registry also supports the data collection requirements in relation to the EMA's exceptional circumstances authorisation of metreleptin.

A new subcutaneous treatment option specifically targeting the underlying cause of lipodystrophy offers significant new hope to patients and their families and carers. Where current supportive care does not address the underlying cause or change the course of the disease, metreleptin offers the potential to mitigate the impact of lipodystrophy and its comorbidities on patients and their carers and in so doing improve both quality and length of life. This will also alleviate the considerable clinical and economic burden on the NHS associated with managing severe metabolic disorders and progressive organ damage, as well as other symptoms such as dysmorphia, hyperphagia, female reproductive dysfunction and depression.

Value for money

A de novo individual patient-level economic model has been developed; it has been designed to align with disease progression and clinical management of the disease. The development has been supported via the Delphi panel consisting of 10 UK and international clinical lipodystrophy key opinion leaders

(23), leveraging established metabolic modelling methodology and findings from the *UK Lipodystrophy Patient and Caregiver Survey*.

The long-term costs and benefits of managing lipodystrophy patients with metreleptin compared to supportive care alone are estimated over a lifetime horizon. A range of lipodystrophy-related complications across multiple organ are captured in six Markov sub-models across the pancreas, liver, heart, kidney, neuropathy and retinopathy. This structure is informed by that of established metabolic models – the Sheffield diabetes model (24), and that cited in NICE non-alcoholic fatty liver disease (NAFLD) guidelines (25) – addressing comments made by the NICE Committee in the previous FED for metreleptin that a diabetes and/or fatty liver disease model capturing disease progression over time would be more appropriate than previous approaches adopted.

Baseline transition probabilities are sourced from the literature and the GL/PL Natural history study. Where direct data for outcomes were not available, the surrogate outcome HbA1c were employed – which is clinically recognised as predictor of disease progression for diabetes-related complications. Clinical effectiveness estimates for metreleptin were sourced from the NIH 991265-20010769 studies for HbA1c, the ITC for the reduction of risk in pancreatitis and the Delphi Panel for the reduction in risk of liver outcomes.

The model incorporates a stopping rule ensuring those that will benefit most from metreleptin are identified based on measures routinely assessed in UK clinical practice. This has been developed with Addenbrooke's Hospital based on their clinical experience from the EAP and the proportion of new patients anticipated to stop treatment. At 9 months after metreleptin initiation, a specialist service review will determine whether treatment should be stopped for PL patients if the following metabolic criteria have not been met: an HbA1c reduction of at least 0.75% from baseline, or a fasting triglyceride reduction of at least 50% from baseline.

Health state costs, patient utilities and caregiver disutilities for lipodystrophy patients sourced from relevant NICE appraisals and guidelines, NHS reference costs, Delphi Panel and published literature.

As part of this submission, a patient access scheme is included reducing metreleptin costs by [redacted] compared to the NHS List price.

After applying a discount rate of 3.5% to both costs and outcomes, patients receiving lipodystrophy accrued an average [redacted] quality-adjusted life years (QALYs) compared to supportive care, at an additional cost of [redacted] per patient. This corresponded to a weighted incremental cost-effectiveness ratio (ICER) of £151,868 per QALY gained across lipodystrophy patients eligible for metreleptin. Patients accrue a hugely meaningful clinical benefit, gaining [redacted] undiscounted QALYs per patient on average. Deterministic and probabilistic and scenario analyses demonstrated that the economic results are robust to changes to key model parameters. The model was most sensitive to changes in clinical transition probabilities and health state utilities.

The estimated number of lipodystrophy patients to be treated with metreleptin in England is expected to rise from [redacted] in year 1 to [redacted] in year 5. It is estimated that the net budget impact of metreleptin in year 1 will be [redacted] rising to [redacted] in Year 5.

Impact of the technology beyond direct health benefits

Lipodystrophy has a devastating impact on patients' health and wellbeing, the breadth and depth of patients' progressive loss of independence and dignity extending to all aspects of their and their carers' lives.

The ability of patients to undertake paid work is significantly reduced by both an impaired ability to work, and impaired schooling. Family members are often carers for lipodystrophy patients, providing medical support and care, and assisting activities of daily living, including household chores such as shopping, cleaning and cooking, as well as daily personal care such as dressing and

bathing. This impacts carers' own ability to work, and their productivity is thus significantly impaired (12).

In addition to the significantly reduced earning potential patients and carers can suffer, the detriment to patients' and carers' ability to undertake everyday activities and actively participate in family life and social activities, and the impact this has on their physical and mental health, is frequently severe.

It is anticipated that metreleptin will fit into the current commissioned clinical pathway via Addenbrooke's Hospital, requiring no additional infrastructure. Home delivery is supported by the manufacturer to ensure patients are able to self-administer metreleptin where preferable and feasible. The introduction of metreleptin will support both patients and the NHS, enabling effective management of lipodystrophy for those patients otherwise unprotected against the risk of complications, and potentially slowing or halting the unrelenting progression of the disease, and the immense burden this can bring.

Summary

Metreleptin is the first and only licensed treatment to target the underlying cause of lipodystrophy and is a safe and effective treatment option for managing GL patients and PL patients for whom supportive care treatments have failed to achieve adequate metabolic control. By reducing the risk of disease progression and multi-organ damage, metreleptin has the potential to reduce premature mortality and improve quality of life and in turn dramatically improve the lives of patients and their carers. A NICE recommendation provides an opportunity to continue treatment in patients with lipodystrophy, in whom metreleptin can address, and is currently addressing, the underlying cause of their disease.

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 1: 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 or partial lipodystrophy	• Adults and children above the age of 2 years with generalised lipodystrophy • Or, adults and children above the age of 12 years with partial lipodystrophy, when standard treatments have failed	Aligns with EMA regulatory approval
Intervention	Metreleptin	Metreleptin as adjunct to diet	In line with NICE final scope; clarification provided for use with diet, in line with licence
Comparator(s)	Established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes)	Supportive care	In line with NICE final scope: Diet lifestyle modifications are a mainstay of disease management irrespective of treatment, and therefore is considered distinct from supportive care. Metreleptin is only licenced

			therapy approved for lipodystrophy
Outcomes	• 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 physical appearance)	• HbA1c (glucose control) and diabetes (including complications of diabetes) • Triglycerides • Liver function (ALT, AST, liver volume cirrhosis) • Hyperphagia (satiety) • Pancreatitis • Use of other drugs • Organ damage including heart, liver and kidneys • Growth and development • Reproductive dysfunction • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	In line with NICE final scope
Nature of the condition	• Disease morbidity and patient clinical	• As per NICE final scope	In line with NICE final scope

	disability with supportive care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options		
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	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access scheme (approved) • The nature and extent of the resources needed to enable the new technology to be used	In line with NICE final scope; an approved patient access scheme is included within this submission
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	As per NICE final scope	-

	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		
Special considerations, including issues related to equality	• If the evidence allows, subgroups according to whether the lipodystrophy is generalised or partial, or congenital or acquired, and according to presence of complications associated with lipodystrophy (including diabetes and hypertriglyceridaemia) will be considered • Guidance will be issued in accordance with the marketing authorisation • Guidance will take any Managed Access Arrangements into account	• Generalised and partial lipodystrophy populations presented as per population criteria above • Guidance will be issued in accordance with the appropriate marketing authorisation • Guidance will take any Managed Access Arrangements into account	Insufficient data available for comparator to allow for any further sub-group analyses

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?

Metreleptin (**met**hionyl **re**combinant human **leptin**) is an analogue of the human hormone leptin. Lipodystrophy is characterised by complete or partial loss or absence of subcutaneous adipose tissue. Adipose tissue plays a key role in energy metabolism and insulin sensitivity through the control of lipid metabolism, which is regulated via the secretion of leptin (26).

Metreleptin binds to and activates the human leptin receptor, a Class I cytokine family receptor, activating various intracellular signalling pathways. This includes Janus kinase 2 (JAK2)/ signal transducer and activator of transcription 3 (STAT3), insulin receptor substrate (IRS)/phosphatidylinositol 3 kinase (PI3K), SH2-containing protein tyrosine phosphatase 2 (SHP2)/mitogen-activated protein kinase (MAPK), and 5' adenosine monophosphate-activated protein kinase (AMPK)/ acetyl-CoA carboxylase (ACC), in the central nervous system and peripheral tissues.

Interestingly, leptin and insulin signalling have similar intracellular pathways and leptin has rapid effects on glucose - it improves glucose tolerance and insulin sensitivity - and lipid metabolism independent of body weight regulation. As such, this reduces the risk of hyperglycaemia and hypertriglyceridaemia (21), and thus reduces the severity and slows the progression of associated diseases and complications such as heart disease, liver disease, pancreatitis, renal failure and insulin resistance.

2.3 Please complete the table below.

Table 2: Dosing Information of technology being evaluated (21)

Pharmaceutical formulation	Powder for solution for injection
Method of administration	Self-administered subcutaneous injection
Doses	3 mg, 5.8 mg and 11.3 mg powder for solution for injection

Dosing frequency	Once daily *Starting dose* The recommended starting daily dose of metreleptin is based on body weight and sex. For males and females weighing ≤40 kg: • 0.06 mg/kg (injection volume: 0.012 mL/kg) For males weighing >40 kg: • 2.5 mg (injection volume: 0.5 mL) For females weighing >40 kg: • 5 mg (injection volume: 1 mL)
Average length of a course of treatment	Chronic therapy, until discontinuation or death
Anticipated average interval between courses of treatments	Chronic therapy, until discontinuation or death
Anticipated number of repeat courses of treatments	Chronic therapy, until discontinuation or death
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), the dose may be decreased, or increased to the maximum dose. For males and females weighing ≤40 kg: • dose adjustments of 0.02 mg/kg are allowed up to a maximum daily dose of 0.13 mg/kg For males weighing >40 kg: • dose adjustments of 1.25 mg to 2.5 mg are allowed up to a maximum daily dose of 10 mg. For females weighing >40 kg: • dose adjustments of 1.25 mg to 2.5 mg are allowed up to a maximum daily dose of 10 mg.

Abbreviations: kg – kilogram; mg – milligrams; mL - millilitre

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).

Metreleptin was granted a marketing authorisation under exceptional circumstances by the European Medicines Agency (EMA) on the 29 July 2018[1]. Metreleptin is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy patients:

- with confirmed congenital generalised lipodystrophy (*Berardinelli-Seip syndrome*) or acquired generalised lipodystrophy (*Lawrence syndrome*) in adults and children 2 years of age and above

- with confirmed familial partial lipodystrophy or acquired partial lipodystrophy (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control (27).

Amyrt Pharmaceuticals DAC acquired Aegerion on 26th September 2019. The Marketing Authorisation transferred from Aegerion Pharmaceuticals BV to Amryt Pharmaceuticals on 28 April 2020.

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

The anticipated date of UK availability is January 2021.

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

Metreleptin was authorised by the EMA under exceptional circumstances on 29th July 2018 and is designated an orphan medicine (21). This authorisation is consistent with the UK marketing authorisation. Metreleptin was authorised by the United States (US) Food and Drug Administration (FDA) on 25 February 2014 (28).

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

Metreleptin has not yet been launched in the UK. However, as part of an Early Access Programme (EAP), treatment with metreleptin in England is currently

[1] The market authorisation holder is currently Aegerion Pharmaceuticals B.V, this will transfer across to Amryt Phama by 17th March 2020.

provided free of charge 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 (29). The service specification is for insulin resistant diabetes, which covers lipodystrophy and includes the use of leptin replacement therapy (29). Further details of the service specification are provided in Section 8.1.

Furthermore, metreleptin is commissioned by NHS England for the use in patients with congenital leptin deficiency under a commissioning policy (reference: 170095P) published in December 2018(30). This is outside the licenced indication and does not form a population that is under consideration in this appraisal.

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.

At the time of submission, Amryt Pharmaceuticals is not aware of any completed or ongoing studies which will provide additional evidence in the next 12 months.

As part of the EMA approval (21), there are requirements for Amyrt to collect further data, which includes a registry and an efficacy study of metreleptin in patients with PL. The registry data planned to be being collected in Europe via European Consortium of Lipodystrophies (ECLip) lipodystrophy disease registry (31). The purpose of the registry requested by the EMA including all patients with generalised or partial lipodystrophy treated with metreleptin is to evaluate the long-term safety and effectiveness of treatment with metreleptin under routine clinical practice. Table 3 summarises the ongoing studies.

Table 3: Ongoing studies relevant to the decision problem

Study Name	Intervention	Population	Objectives	Reference
QuaLip		N=75 Baseline analysis covers adult patients (n=67) • CGL: n=15 • APL: n=10 • FPLD: n=42	This study is designed to explore metreleptin naïve lipodystrophy patients' experience of lipodystrophy (LD) including the subjective burden of the disease, and how it changes over time. The study will explore the impact on adult patients as well as	Data on file

			children and young people. • To identify a core set of outcome measures to include in an assessment of the subjective burden of lipodystrophy • To measure any change in subjective burden over time.	
Addenbrooke's data collection	Metreleptin	Patients with GL or PL (as per metreleptin licence)	To collect data in patients with GL or PL who are administered metreleptin post-publication of a NICE recommendation at the main centre for care for patients with lipodystrophy. This will include metabolic outcomes and long-term complications associated with lipodystrophy at baseline and every year.	Data on file
ECLip LD Disease Registry	Metreleptin, Supportive care	Minimum 246 patients	The registry aims to provide the basis for an improved estimate of the prevalence of lipodystrophy, patient-centred clinical lipodystrophy research, e.g. for instance on the natural course of disease, management strategies and outcomes. This registry has been set-up in response to the EMA's exceptional circumstances authorisation of metreleptin.	(21,31)

Abbreviations: APL – Acquired partial lipodystrophy; CGL – Congenital generalised lipodystrophy; EMA – European Medicines Agency; FPLD – Familial partial lipodystrophy disease; GL – Generalised lipodystrophy; LD – lipodystrophy; PL – Partial lipodystrophy

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).

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**

Amryt Pharmaceuticals DAC does not believe that there are any equality issues relevant to this evaluation.

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

Not applicable – no potential equality issues have been identified.

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

Lipodystrophy is an ultra-rare, progressive, chronic disease composed of a heterogeneous group of congenital or acquired disorders associated with complete or partial loss of adipose tissue (2). The absence of subcutaneous adipose tissue leads to a decrease in the level of endogenous leptin and a reduction in the individual's storage capacity of lipids, which accumulate ectopically in other organs (32,33).

Leptin deficiency, and the resultant lack of adipose tissue, leads to the early development of serious metabolic disorders such as insulin resistance leading to diabetes (defined as HbA1c level >6.5%) or hypertriglyceridaemia (defined as triglyceride [TG] level >200 mg/dL, [>2.26mmol/L]) (2,5–7), which are generally difficult to manage as they are refractory to conventional treatment with hypoglycaemic and hypolipemic agents (5).

The complications resulting from these metabolic disorders together with ectopic lipid deposition in various organs can lead to early development of cardiovascular complications and multi-organ damage that may become irreversible in organs such as the liver (hepatic steatosis, cirrhosis, liver failure), kidneys (nephropathy, proteinuria, renal failure) and pancreas (acute pancreatitis), leading to high morbidity, impaired quality of life and premature death (2,10,11).

The prevalence of the disease has been estimated worldwide at 0.2-1.0 cases/million for GL and 1.7-2.8 cases/million for PL (34). In the UK, Addenbrooke's Hospital is the only Reference Centre for Lipodystrophy has registered [redacted] patients with active lipodystrophy ([redacted]).

The diagnosis of lipodystrophy – based on the history, physical examination, distribution of body fat tissue and metabolic state of the patient – is complex (35). Genetic testing or analysis of blood leptin levels neither confirm nor discount the presence of lipodystrophy. The difficulty of diagnosis together with the low recognition of the disease (due to its rarity and low exposure to

clinicians) leads to many patients being diagnosed late when the course of the disease is advanced and the multi-organ damage may be irreversible (2,5).

6.1.1.1 Generalised lipodystrophy

Congenital Generalised Lipodystrophy (CGL)

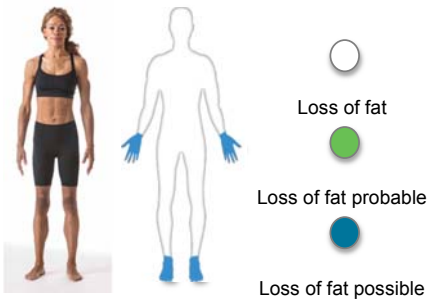
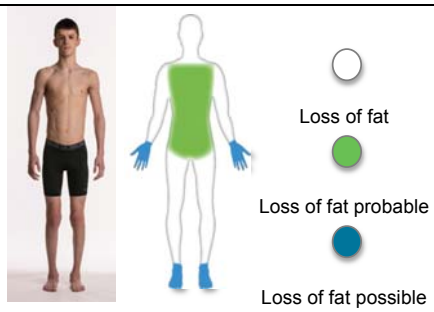
CGL, also known as Berardinelli-Seip Syndrome (BSS), is an autosomal recessive disorder characterised by a generalised lack of subcutaneous adipose tissue starting at birth or infancy (2). In addition, it is typical for patients with CGL to display umbilical prominence, muscular appearance with prominent veins, hepatomegaly, splenomegaly, and precocious puberty (2). The lack of subcutaneous adipose tissue leads to a leptin deficiency, limited triglyceride energy storage capacity, and ectopic fat accumulation in organs and muscles in lipodystrophy patients (32). Multiple genetic causes have been identified, each with unique clinical features (2) which are displayed in Table 4.

Acquired Generalised Lipodystrophy

AGL, also known as Lawrence syndrome, is characterised by a generalised lack of subcutaneous adipose tissue – however, in contrast to CGL, patients with AGL are born with normal fat distribution but progressively lose fat in a generalised fashion (5). The loss of adipose tissue occurring in childhood or adolescence, preceded or followed by autoimmune or inflammatory manifestations and three subtypes of AGL (panniculitis, autoimmune, and idiopathic) have been proposed. Additionally, lymphoma has been reported to be associated with AGL and an increased risk of malignancy in these individuals - may be attributable to autoimmune disease – has been reported (35). AGL appears to be more common in females (by a ratio of 3 to 1) (2).

The causes of AGL are not fully known. Patients with AGL exhibit similar clinical features to CGL, including severe lack of subcutaneous adipose tissue, hepatomegaly, splenomegaly, diabetes, hirsutism and hyperphagia.

Table 4: Essential Features of Generalised Lipodystrophy

Type	CGL	AGL
Adipose tissue distribution		
Mean age of onset	0.3 years (range 0–12)	5 years (range 0–15)
Gender distribution (female:male)	2:1	3:1
Physical Features	• Near complete lack of adipose tissue • Muscular appearance • Prominent veins • Umbilical prominence • Precocious puberty • Acanthosis nigricans • Hirsutism (in females)	• Progression of fat loss • Hyperkeratosis • Enlarged liver • Hirsutism
Clinical Features	• Hepatomegaly • Splenomegaly • Diabetes mellitus • Irregular menstrual periods, hyperandrogenism, polycystic ovaries, and/or infertility in females	• Hepatomegaly • Splenomegaly • Diabetes mellitus • Hypogonadism • Presence of autoimmune diseases or panniculitis
Subtypes (causes and effects)	• CGL1: AGPAT2 mutations- Patients lack metabolically active fat • CGL2: BSCL2 mutations - Most severe form, patients lack mechanical and metabolically active fat; they may also suffer from mental retardation • CGL3: Caveolin 1 (CAV1) mutations - Associated with short stature and vitamin D resistance, only one patient known • CGL4: Polymerase I and transcript release factor (PTRF)	• Not fully known

	mutations - Extreme lack of body fat, associated with pyloric stenosis	
Abbreviations: AGL, acquired generalised lipodystrophy; AGPAT2, 1-acylglycerol-3-phosphate O-acyltransferase 2; CAV1, caveolin 1; CGL, congenital generalised lipodystrophy; BSCL2, Berardinelli-Seip type 2; GL, generalised lipodystrophy; PTRF, polymerase I and transcript release factor		

Source: Amryt, data on file, 2017 (3); Gupta, 2017 (14); Handelsman, 2013 (5); Garg, 2011 (36); Agarwal, 2003 (37); Brown, 2016 (2).

6.1.1.2 Partial lipodystrophy

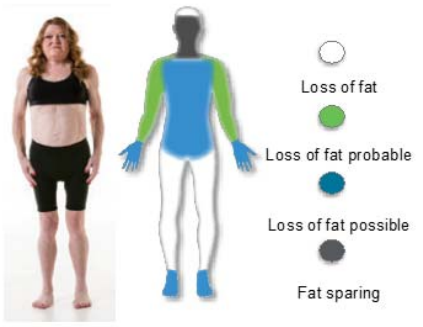
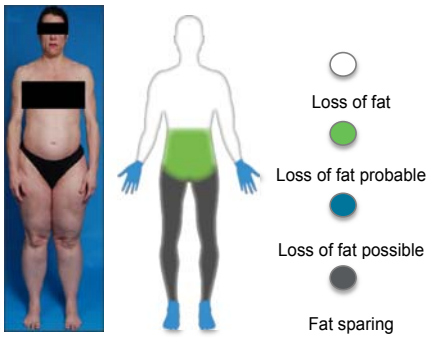
Familial Partial Lipodystrophy (FPL)

FPL is characterised by the regional loss of subcutaneous adipose tissue. Patients with FPL usually have normal body fat distribution up until the beginning of, or after, puberty, at which point patients will develop the progressive loss of fat in the arms and legs resulting in a peripheral muscular appearance and variable fat loss in the abdomen and chest according to subtype (5). There are various subtypes of FPL, including FPL1 (Köbberling variety), FPL2 (Dunnigan variety), all the way through to FPL7, the causes and effects of which are described in Table 5.

Acquired Partial Lipodystrophy (APL)

APL, also known as Barraquer-Simons Syndrome, is distinguishable from other lipodystrophy syndromes by the unique cephalocaudal progression of subcutaneous fat loss that is observed (38). It is a very rare disorder. Loss of subcutaneous adipose tissue begins in the face, and then spreads to the neck, upper extremities, thorax, and abdomen over a period of months or years. In addition, APL is more common in females (by a ratio of 4 to 1) and typically develops during childhood or adolescence (5).

Table 5: Essential Features of Partial Lipodystrophy

Type	FPL	APL
Adipose tissue distribution		
Mean age of onset	9.9 years (range 0–16)	8.2 years (range 0.5–16)
Gender distribution (female:male)	2:1	4:1
Physical Features	• Regional loss of adipose tissue, usually around puberty, may resemble obesity or Cushing's Syndrome • Acanthosis nigricans • Hirsutism (in females)	• Fat loss occurs in cephalocaudal fashion • Fat accumulation around the hips or legs
Clinical Features	• Hepatomegaly • Hyperphagia • Diabetes • Hyperandrogenism (in females)	• Main cause of morbidity is chronic renal disease • Associated with a number of autoimmune diseases including dermatomyositis and systemic lupus erythematosus
Subtypes (causes and effects)	• FPL1: Unknown cause - Loss of gluteal and limb fat, but leptin levels often unaffected • FPL2: Lamin A/C mutations – Fat accumulation around neck and reduced leptin levels • FPL3: Peroxisome proliferator activated receptor gamma (PPARG) mutations • FPL4: Perilipin 1 (PLIN1) mutations	• Not fully known

	• FPL5: Cell-death-inducing DNA, fragmentation factor a-like effector c (CIDEC) mutations • FPL6: Adrenoceptor alpha 2A (ADRA2A) mutations - Fat accumulation around neck • FPL7: Hormone-sensitive lipase (LIPE) mutations	
Abbreviations: ADRA2A, Adrenoceptor alpha 2A; APL, acquired partial lipodystrophy; CIDEC, Cell-death-inducing DNA, fragmentation factor a-like effector c; FPL, familial partial lipodystrophy; LIPE, Hormone-sensitive lipase; PL, partial lipodystrophy; PLIN1, Perilipin 1; PPARG, Peroxisome proliferator activated receptor gamma		

Source: Amryt, data on file, 2017 (3); Gupta, 2017 (14); Handelsman, 2013 (5); Garg, 2011 (36); Brown, 2016 (2)

6.1.2 Underlying course of the disease

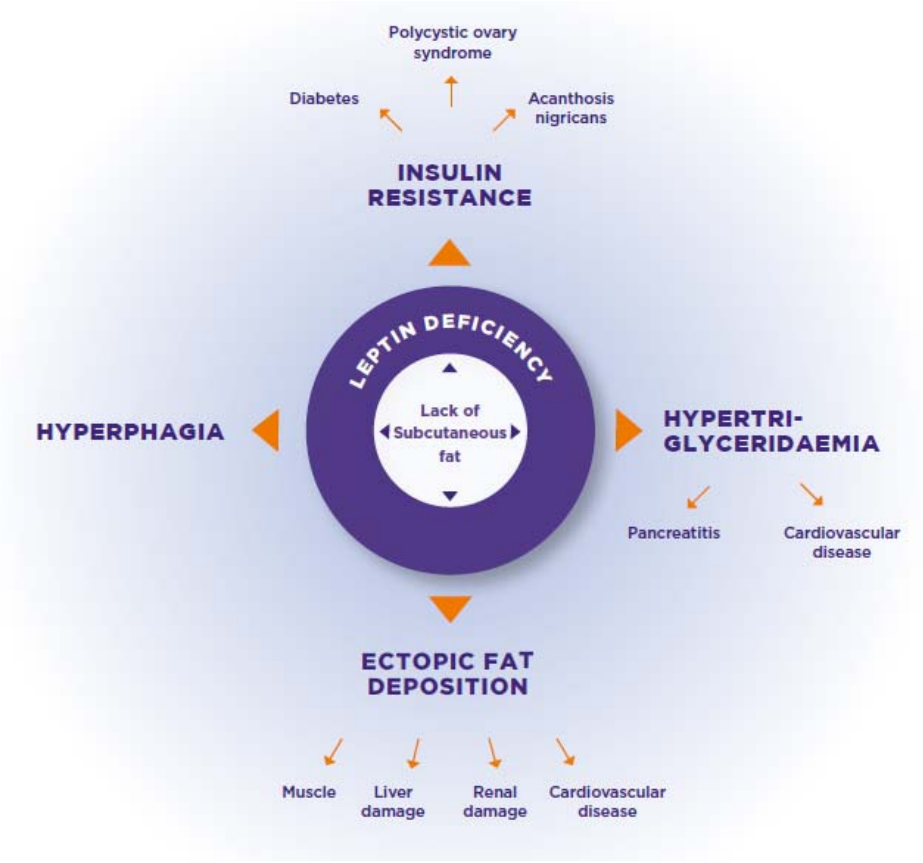
The primary feature of lipodystrophy syndromes is the loss of subcutaneous adipose tissue. The essential metabolic hormone leptin, which is produced by adipose tissue and also known as the satiety hormone, plays a pivotal role in energy homeostasis, neuroendocrinology, and metabolism (3,4). The loss of adipose tissue and resulting leptin deficiency and reduced fat storage capacity leads to numerous metabolic complications (

Figure 1). Adipose tissue is the body's single most important energy storage site, with excess lipids being primarily stored in the form of triglycerides (3,39). With adipose tissue loss, storage capacity for triglycerides is easily exceeded, leading to ectopic fat accumulation in non-adipose tissue, including the musculature and organs such as the liver, heart, kidney and the pancreas, insulin resistance, hyperglycaemia, hard to treat diabetes and severe hypertriglyceridaemia. Excess triglycerides accumulate ectopically in non-adipose tissue, which may lead to direct lipotoxicity and patient morbidity at a young age.

Adipose tissue also plays a leading role in energy metabolism and insulin sensitivity through the control of lipid metabolism and the secretion of leptin (3). The metabolic consequences of a loss of adipose tissue are driven by the loss of leptin secretion which adversely affect appetite control (hyperphagia), immunological and hormonal impairments, and metabolic dysfunction (

Figure 1).

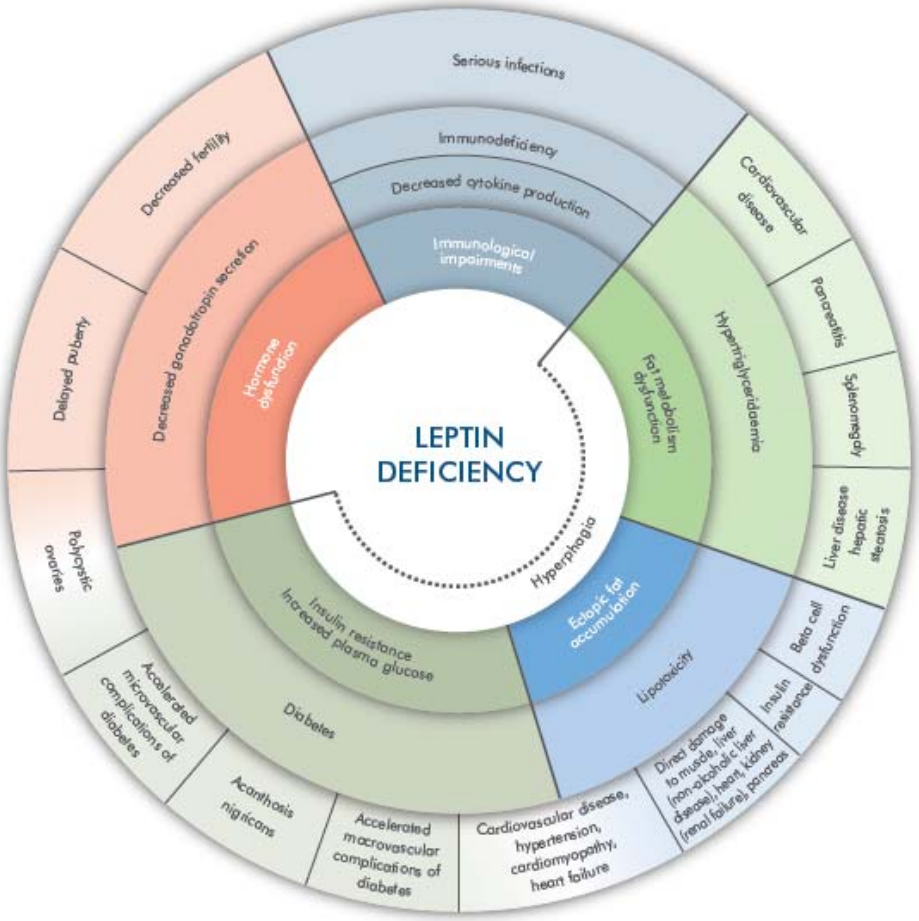
Figure 1: Consequences of adipose tissue loss



Source: Amryt, data on file, (2019) (40)

Leptin has multiple roles in normal physiology including the protection of peripheral tissues from lipotoxicity and regulating fatty acid metabolism (41). Figure 2 illustrates the multiple metabolic and endocrine issue caused by leptin deficiency which are often severe and can have potentially life-threatening consequences.

Figure 2: Clinical consequences associated with leptin-deficient lipodystrophy



Source: Amryt, data on file (3)

6.1.3 Disease morbidity and mortality

This section provides further details on the range of complications, which includes:

- Pancreas complications
- Liver disease
- Heart disease
- Renal disease
- Insatiable hunger and hyperphagia
- Physical appearance

- Precocious puberty and Infertility
- Premature mortality

The loss of adipose tissue and resulting ectopic accumulation of lipids throughout the body can cause severe insulin resistance (15). Insulin resistance in turn leads to a host of conditions including hard to treat diabetes and hypertriglyceridaemia. Indeed, risk factors for type 2 diabetes include dyslipidaemia and hypertriglyceridaemia (42), both of which are clinical characteristics of lipodystrophy (2). In a recent longitudinal study, diabetes/insulin resistance was identified in 58.3% of GL and PL patients (n=230) (15). The complications associated with diabetes, such as cardiovascular disease, retinopathy and neuropathy, are described in further detail below.

Pancreas complications

6.1.3.1.1 Pancreatitis

Patients with lipodystrophies are predisposed to developing acute pancreatitis (36) which is associated with increased mortality (43). Hypertriglyceridaemia is an important aetiology for acute pancreatitis, with data suggesting hypertriglyceridaemia-associated acute pancreatitis results in worse clinical outcomes than other acute pancreatitis associated aetiologies (44). This is supported by Akinci *et al* (45) who reported that 12.5% of GL patients reported pancreatitis over their lifetime. Similarly, baseline characteristics of the cohort in the QuaLip study reported that 17.91% of the adult population in the cohort (n=67) were diagnosed with pancreatitis. The NIH follow up study found that prior to metreleptin treatment 39.3% of patients had a diagnosis of acute pancreatitis, and after metreleptin treatment this number reduced drastically to only 0.9% of the patient population having a diagnosis of acute pancreatitis.

6.1.3.2 Liver disease

Ectopic fat deposition in the liver and muscle can progress to hepatomegaly, steatohepatitis, portal hypertension, cirrhosis and liver failure (46). Liver disease in all its forms (liver failure, gastrointestinal haemorrhage, hepatocellular carcinoma) is considered a major cause of mortality in lipodystrophy patients (2). Clinical experts have highlighted that the liver disease complications observed are analogous to that associated with non-alcoholic fatty liver disease (NAFLD).

A large retrospective review of liver damage in lipodystrophy by Akinci *et al.* (47) found that the liver was the most commonly damaged organ. Among metreleptin-treated patients (68 GL; 44 PL), damage was present in 91.1% of

GL and 72.9% of PL patients prior to treatment. In metreleptin-naïve patients (56 GL; 122 PL), liver damage was present in 94% of GL patients and 73% of PL patients. The most recent and largest review by Akinci *et al.* (15) again found that liver abnormalities (including hepatic steatosis, hepatomegaly, cirrhosis) were the most common organ abnormality (overall sample n=230; 71.7%, GL subgroup n=81; 87.7%, PL subgroup n=149; 63.1%).

6.1.3.3 Heart disease

The reduced storage capacity in adipose tissue leads to excess triglycerides accumulating ectopically in non-adipose tissue. Elevated triglyceride levels are a known risk factor for cardiovascular disease (48). In addition, the resulting leptin deficiency of adipose tissue loss impacts insulin resistance, which in turn increase HbA1c levels and hard to treat diabetes and thus associated with cardiovascular disease, cardiomyopathy and heart failure (Figure 2). Heart abnormalities, such as coronary heart disease, cardiomyopathy, and heart failure, have been reported to occur in 30.4% of lipodystrophy patients.

6.1.3.4 Renal disease

Kidney abnormalities are common in lipodystrophy patients as a result of ectopic fat accumulation in the kidneys and the lipotoxicity that occurs from this (Figure 2). Akinci *et al.*, in a longitudinal medical chart review study of 56 GL patients found kidney abnormalities occurred in 50% of patients, including kidney failure (7.1%) and nephropathy (42.9%) (45). Proteinuria is a type of nephropathy and is a frequent finding in patients with lipodystrophy (2,49).

In a separate, larger study of 230 GL and PL patients, kidney abnormalities were found in 40.4% of patients. Specifically, 32.2% experienced nephropathy, 4.3% chronic renal failure, 3.5% End Stage Renal Disease (ESRD), 0.4% kidney transplant, and 12.2% other (including haematuria, kidney stones, nephromegaly, renal hypoplasia) (15).

6.1.3.5 Insatiable hunger and hyperphagia

Patients with lipodystrophy, especially generalised forms, are typically hyperphagic (2). Leptin is a satiety signal, therefore low leptin levels act on the brain as a starvation signal; patients with lipodystrophy often suffer from to have insatiable hunger and consecutive hyperphagia which causes distress to themselves and caregivers alike. Hyperphagia, on the other hand, leads to an increased caloric intake that, in turn, worsens the metabolic situation and ectopic fat accumulation (3).

6.1.3.6 Physical appearance

The partial and generalised loss of subcutaneous fat and abnormal fat distribution can have marked effect on the physical appearance of patients with

GL and PL which causes distress and reduces quality of life (8). Details of fat distribution and physical features across lipodystrophy type are described in Table 4 and Table 5.

6.1.3.7 Precocious puberty and Infertility

Leptin regulates secretion of gonadotropins and gonadal steroids which influences puberty and fertility. Leptin deficiency from lipodystrophy thus impacts hormonal balance such that oligo/amenorrhea, decreased fertility, and polycystic ovary syndrome (PCOS) are common in female partial lipodystrophy patients. Additionally, early adrenarche, true precocious puberty, or central hypogonadism may occur in children with generalised lipodystrophy (2).

6.1.3.8 Premature mortality

In a systematic review, the mean age of death is 12.5 years for patients with CGL, 32.2 years for AGL, 27.8 years for FPL and 22.7 years for APL (14). Additionally, in a large study by Akinci *et al.* (15) the average age of death for patients with GL is 33.8 years and 53.9 years for patients with PL, demonstrating significant premature mortality. Contributing factors to death included cardiovascular events, liver disease and pancreatitis.

In a multinational cohort of patients not treated with metreleptin, mortality of patients with GL is 23.9% at 40 years and 36.6% at 60 years. The leading causes of death were end-stage liver disease, the most common potential factor of death, followed by end-stage renal disease, heart failure, and acute pancreatitis (16).

6.1.3.9 The Patient Need

The current management paradigm for patients with lipodystrophy has been focused upon symptom management via supportive care including diet and exercise, conventional therapies for hyperglycaemia and hypertriglyceridaemia. Brown reports that lipodystrophy patients are refractory to conventional treatments, especially anti-hyperglycaemic agents, resulting in the use of very high insulin doses which are ineffective to achieve adequate diabetes control in many lipodystrophy patients and is simply impractical in a clinical context (13). This leaves patients at higher risk of disease complications across multiple organs and premature mortality.

Metreleptin is the first and only causal treatment option to treat the complications of leptin deficiency in lipodystrophy patients, which has demonstrated its efficacy and long-term safety, improving survival outcomes by delaying the progression of organ damage. The improvements observed with metreleptin treatment at the metabolic level and in other comorbidities are associated with a statistically significant decrease in the risk of disease

progression by >50% and >70% in the risk of mortality compared to those patients not treated with leptin replacement therapy (50).

In addition, the benefit of metreleptin for paediatric patients should be noted. The prognosis in these patients without adequate treatment is often severe due to early development of complications and multiorgan damage. Metreleptin has demonstrated its efficacy and long-term safety in paediatric patients, which justifies its early intervention given the progressive nature of the disease without treatment, providing a high benefit in preventing the occurrence of organ damage and disease progression, as evidenced in the multi-society practice Guidelines for the Diagnose and Management of lipodystrophy (2,21).

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 lipodystrophy in England. However, there are relevant and accurate estimates available based on Early Access Programme (EAP) data from a decade of metreleptin use in UK clinical practice at Addenbrooke's.

[redacted] lipodystrophy patients are currently receiving metreleptin at Addenbrooke's under the EAP – [redacted] patients with GL and PL, respectively. 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 13.1 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.

There is no evidence to indicate the life expectancy of lipodystrophy patients in the UK, although it is expected data from other countries to be generalisable to the UK. The complications of lipodystrophy are serious and have catastrophic consequences leading to premature mortality, occurring at young ages in some cases. In a systematic review, the mean age of death is 12.5 years for patients with CGL, 32.2 years for AGL, 27.8 years for FPL and 22.7 years for APL (14). The data below is sourced from an international chart review which obtained

patient medical charts at five treatment centres across three countries (Brazil, Turkey and US). The loss of adipose tissue and resulting ectopic accumulation of lipids throughout the body can cause severe insulin resistance and other metabolic abnormalities, which can lead to organ damage and higher rates of mortality, especially in GL. In a large study by Akinci et al (15) the average age of death for patients with GL is 33.8 years and 53.9 years for patients with PL, demonstrating significant premature mortality. Contributing factors to death included cardiovascular events, liver disease and pancreatitis. Full details are listed in Table 6.

Table 6: Mortality events by contributing factors

Study group	n/N[a] deaths (%)	Age at death mean (SD)	Contributing factor[a] (n)
GL N=81	10/81 (0.12)	33.8 (17.0)	Bone marrow/hematologic abnormalities (1), Cardiovascular event (4), Cerebrovascular disease (1), Immunosuppression (1), Infection (bacterial) (3), Liver disease (3), Pancreatitis (2), Pneumonia (2), Renal failure (1), Sepsis (1), Unknown (1), Other[b] (1)
PL N=149	8/149 (0.05)	52.9 (14.7)	Cardiovascular event (2), Cerebrovascular disease (2), Liver disease (1), Renal failure (1), Unknown (4)

[a] More than one contributing factor may be selected for each mortality event and may be different from the reported cause(s) of death noted inpatient records.

[b] Other potential contributing factors of death included mentions of pancytopenia, steatohepatitis, and chronic renal insufficiency.

Abbreviations: GL, generalised lipodystrophy; PL, partial lipodystrophy; SD, standard deviation

Source: Akinci, 2019, (15)

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).

Lipodystrophy has a detrimental impact on patients' and their carers' quality of life (QoL). A study by Dhankhar *et al.* (2015) (51) evaluated the health related quality of life (HRQoL) of lipodystrophy patients from the Lipodystrophy Connect Registry and reported that the average estimated EQ-5D score associated with lipodystrophy was 0.67 (SD: 0.11), much lower than the average EQ-5D of the general population (0.866). For context, the EQ-5D of diabetes-related complications range from 0.70 to 0.79 (52). Due to the limited evidence available, additional interviews and surveys have been undertaken to provide further understand of the burden of the disease on patients and their carers, including:

1) *Lipodystrophy Patient and Caregiver Survey* – an interview-based study with patients with lipodystrophy was conducted in order to ascertain the perspective of US and UK adult patients with lipodystrophy and their caregivers. The quantitative impact of the disease on quality of life was assessed via SF-36.

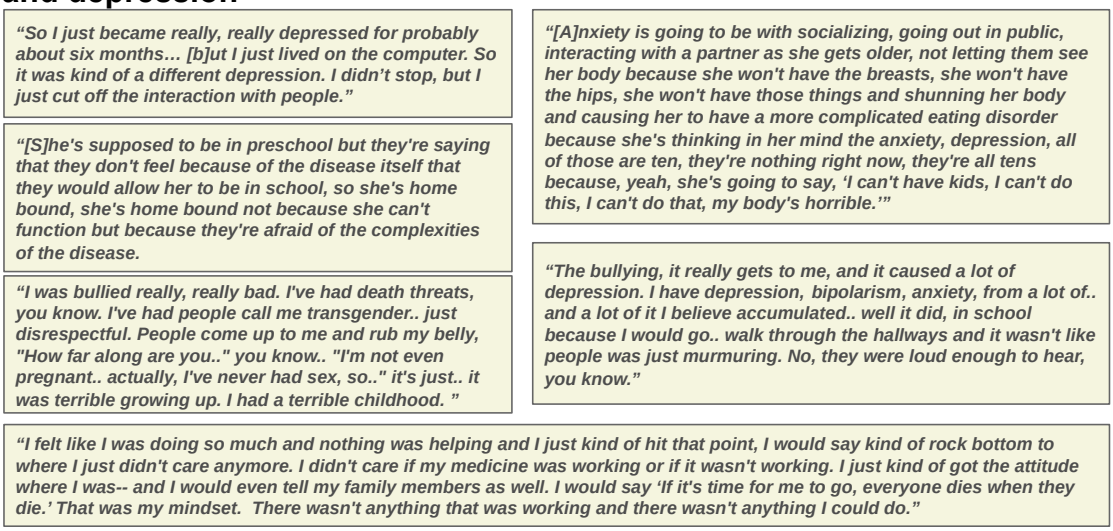
2) *Lipodystrophy Caregiver Disease Burden Survey* – consisting of a combination of self-completed questionnaires and moderator administered interviews with caregivers of patients with lipodystrophy in the UK, exploring carers experience and the impact on day to day life of caring for someone with lipodystrophy. The quantitative impact of carer burden was assessed via the Zarit Caregiver Burden Interview (ZBI). Health related quality of life was assessed through the EQ-5D.

7.1.1 Emotional wellbeing

The psychological and emotional impact of lipodystrophy is substantial. Patients often experience anxiety and depression due to the clinical manifestations of the disease, including impaired physical appearance and subsequent dysmorphia, reproductive dysfunction, fatigue and hyperphagia. For instance, a study exploring the psychiatric assessment of women with lipodystrophy revealed an increase prevalence of mood, anxiety, pain and eating disorders compared to the general population (9). Furthermore, laboratory indicators of the disease such as low leptin levels and increased HbA1c are associated with symptoms of depression (53,54). 50% of patients were found to score lower (worse) than the general population average on that

Mental Component Summary (MCS), a component of the Short-Form 36 (SF-36) survey (8). Figure 3 shows selected quotes illustrating the symptoms of depression and anxiety associated with lipodystrophy.

Figure 3: Selected quotes in lipodystrophy patients and carers: Anxiety and depression



Source: Amryt, data on file (55)

7.1.1.1 Impaired physical appearance

84% of lipodystrophy patients reported altered physical appearance as an attribute they considered a disease-related complication (8), including muscularity of arms and legs, excessive facial hair, acanthosis nigricans or an acromegaloid appearance (Table 7).

These changes can cause both psychological distress and physical discomfort (2). As a result of their altered physical appearance, patients may experience bullying and low self-esteem. *The Lipodystrophy Patient and Caregiver Survey* reported that physical appearance – such as excess muscles - was a barrier to developing new relationships, leading to social withdrawal, isolation and increasing feelings of anxiety and depression. One patient reported the effect her physical appearance inflicted on her psychological well-being in particular (8):

> *"[…] Because* [my physique] *makes other people uncomfortable, it makes me uncomfortable. And I think that's what-- it's the bullying-- it's all psychological for me. Like I don't think it's more so my condition that I'm sick, it's psychological, because it's like, "Okay, I love myself" […] But then when I go out to the world, where everybody else is different, it kind of makes me feel like an outcast."*

Table 7: Illustrations of impaired physical appearance in lipodystrophy

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 (left) or, differentially, LD in face, neck, thorax and arms with fat accumulation in hips that can be seen in some Barraquer-Simmonds syndrome (right)	

7.1.1.2 Hyperphagia

Hyperphagia was reported as a disease-related attribute in 92% of patients and is thought to have a substantial impact on the psychological wellbeing of lipodystrophy patients (8). Due to the subjective state of excessive hunger it is difficult to capture quantitatively, though it has been likened to a state of starvation ("*Sometimes since we're so hungry we'll binge, binge, binge […], so yeah it's terrible… starving all the time")* (8), to the extent of distracting from day-to-day activities:

> *"Just really excess hunger that took my focus away from school, from whatever activities I was engaged in […] my temper was very, very, very short, I think. I was always on edge because I was so hungry"*

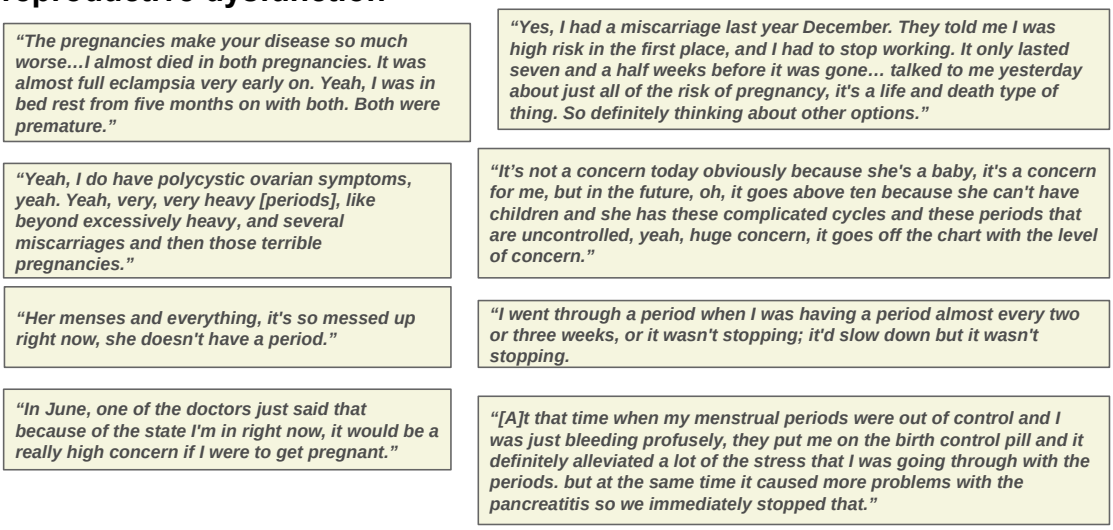
> *"It* [hunger] *was pretty constant and very severe, in that I really couldn't focus on anything but that feeling"* (8)

7.1.1.3 *Reproductive issues*

The effect of lipodystrophy and subsequent leptin deficiency on reproductive health was found to be a considerable source of anxiety. The source of this anxiety varied, including concerns regarding infertility, high-risk and life-threatening pregnancies, and miscarriages (8). 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 individuals' psychological and interpersonal functioning. PCOS symptoms can lead to significant deterioration in QoL and be highly stressful, negatively affecting psychological well-being. Following miscarriage, women can experience post-traumatic stress, anxiety and depression. Interviews with patients with lipodystrophy confirm the impact of reproductive dysfunction (Figure 4).

Figure 4: Selected quoted in lipodystrophy patients and carers: reproductive dysfunction



Source: Amryt, data on file (55)

Patients of a childbearing age were found to express feelings of anxiety, guilt and responsibility about passing the disorder onto their children (8):

> *"For me finding out that my daughters also had it, that was a big thing in my life, because I just felt so guilty, […]* [I] *worry about my brothers' health quite a bit… I have been nagging them to get a blood test done to find out if they do have it to get the official diagnosis, but I do worry about their health. It upsets me when my daughters reach a point where they start to deteriorate in something. That does affect me a lot, because it brings back the guilt feeling, although it's ridiculous, I know, but it's like if I'd have known I would have done something about it, not had children or got them tested."*

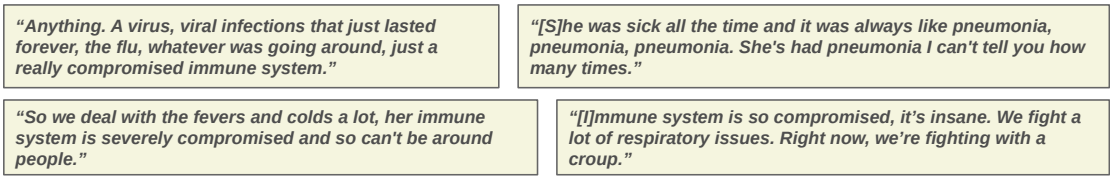
7.1.2 Physical health

Physical attributes of lipodystrophy contributing to a decreased quality of life include hard to treat diabetes and severe hypertriglyceridaemia and the increased risk of associated complications across ranging from heart disease, liver cirrhosis, chronic pain, amputation and kidney disease. 70% of lipodystrophy patients surveyed scored less (worse) than the general population in the Physical Component Summary (PCS) of the SF-36 (8). *The Lipodystrophy Patient and Carer Survey* reported that patients were concerned

with the risk of organ damage, with 75% of patients interviewed exhibiting symptoms of organ damage (8). As the disease progresses and damage and complications across one or more organs accumulate, further deterioration of quality of life occurs – ultimately resulting in premature mortality in patients with lipodystrophy through the risk of death associated with organ-specific symptoms and eventual organ failure, for example hepatomegaly leading to liver disease, and macroalbuminuria leading to renal failure (56).

Furthermore, a compromised immune system leading to frequent illness and infection may lead to a decreased quality of life not only in their own right, but also through individuals avoiding social interaction due to a fear of illness or infection, compounding feelings of social isolation (8) (Figure 5).

Figure 5: Selected quoted in lipodystrophy patients and carers: compromised immune system



Source: Amryt, data on file (55)

7.1.3 Everyday life

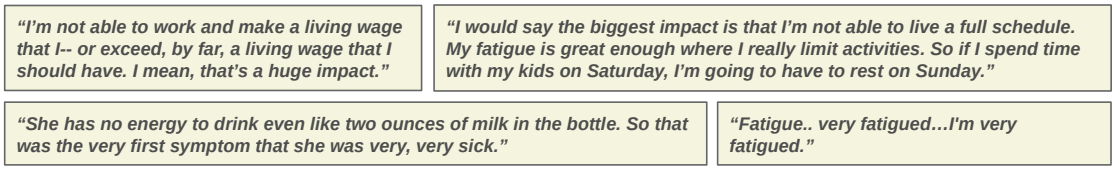
Lipodystrophy has been found to considerably impact patients' independence and sense of normality in everyday life, including their ability to work and study. In particular, fatigue may lead to an impaired ability to work, study, and carry out day to day activities (Figure 6) (12):

> *"… She has become withdrawn and has lost confidence. I do all the driving, I help her walk, I deal with her medication and help her take them. I take her out and accompany her shopping, cooking and remind her of appointments. I now take care of all financial aspects of our life…"*

> *"… I help her when she is really tired – I pick her up from work, do the dinner, walk the dog, go with her to hospital appointments, being there for her when she is feeling low. I also do her emails and her paperwork."*

In particular, fatigue may lead to an impaired ability to work, study, and carry out day to day activities (Figure 6).

Figure 6: Selected quotes in lipodystrophy patients and carers: fatigue (55)



Source: Amryt, data on file (55)

In a survey of 5,000 people across 48 European countries living with a rare disease, 55% of the patients experienced a severe or very severe impairment in carrying out daily tasks. (57) This is reflected in the *Lipodystrophy Patient and Carer Survey,* with patients reporting that the pain associated with lipodystrophy associated symptoms – such as advanced bone age, neuropathy, irregular menstrual cycles and muscle spasms - was identified as a barrier to carrying out day to day tasks, such as household chores, exercise and running errands (8):

> *"So I can't do all of what I used to be able to do. For example, if I do housework I've got to do kind of little bits at a time rather than do it all in one go."*

7.1.4 Carers

Carers often suffer from many of the complications that individuals with lipodystrophy experience, from deterioration of mental health to a reduced quality of day to day life. The impact of lipodystrophy on caregivers also leads to an economic burden due to reduced household income, a time burden and social stigma.

7.1.4.1 Emotional wellbeing

The *Lipodystrophy Caregiver Disease Burden Survey* reported a substantial psychological and emotional burden for carers of patients with lipodystrophy. 43% of carers of patients with lipodystrophy indicated feeling anxious or depressed (12). 100% of carers interviewed reported providing some degree of emotional or social support. The degree of 'personal strain', assessing questions such as whether carers feel angry around relatives, feelings of uncertainty and inability to cope was the highest scoring ZBI domain, achieving a score of 19 out of 36 (12).

The *Lipodystrophy Patient and Carer Survey* reported that caregivers expressed guilt and anxiety due to their lack of preparedness to care for a lipodystrophy patient (8):

"I think I was so crushed when she was diagnosed, so that had a huge impact on my mental health as well and so that was, like, a huge hit, like a huge truck…"

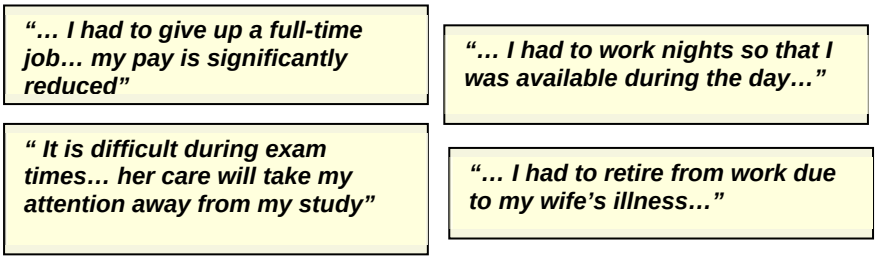
7.1.4.2 Physical health

The *Lipodystrophy Caregiver Disease Burden Survey* reported that 43% of carers felt that their own health issues had been neglected due to their caring responsibilities, with 71% of carers feeling that the needs of patients with lipodystrophy come before themselves and 43% of patients indicated feeling some degree of pain and discomfort (12).

7.1.4.3 Everyday life

Carers' everyday life is substantially affected due to lipodystrophy complications. Social isolation may arise due to members of family being limited in their ability to work or socialise due to caring responsibilities. In the *Lipodystrophy Caregiver Disease Burden*, many caregivers expressed feelings of sacrificing aspects of their day to day life in order to help patients:

Figure 7: Selected quotes in lipodystrophy carers: changes to responsibilities



Source: Amryt, data on file (12)

Many of the symptoms experienced by lipodystrophy patients, such as fatigue, ultimately result in social isolation, for both patients and carers (12):

"… She has become withdrawn and has lost confidence. I do all the driving, I help her walk, I deal with her medication and help her take them. I take her out and accompany her shopping, cooking and remind her of appointments. I now take care of all financial aspects of our life…"

"… I help her when she is really tired - I pick her up from work, do the dinner, walk the dog, go with her to hospital appointments, being there for her when she is feeling low. I also do her emails and her paperwork."

A summary of the impact on QoL associated with lipodystrophy is shown in Table 9. 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 8: Range of complications and impact on QoL associated with lipodystrophy

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.
Triglyceride control	• Hypertriglyceridaemia • Hypercholesterolaemia	• Need for extra medication (e.g. hypertriglyceridaemia) • Organ damage • Increased risk of stroke, heart disease and heart attack • Higher than normal mortality risk 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 • Anxiety • 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	• Disruption of day to day life ("…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")
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 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
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/schoolwork	• Impaired or complete inability to work or attend school due to: o Fatigue o Hyperphagia o Bullying (e.g. due to physical appearance) o Frequent infection/illness	• Detrimental impact on education • Low wages/poor work prospects • Need to take unpaid leave • Inappropriate socialisation • Depression/anxiety
Psychological complications	• Impaired physical appearance • Chronic pain • Anxiety • Depression • Fatigue	*"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: 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 group(s) of patients, and their families or carers.

The prognosis in lipodystrophy patients without adequate treatment is often severe due to early development of complications, multiorgan damage and associated degraded QoL (2,21). Metreleptin treatment is effective at improving metabolic abnormalities associated with lipodystrophy, slowing disease progression and resulting in a reduction in the risk of associated complications, with leptin replacement therapy being associated with quality-adjusted life years (QALY) gains of 0.313 and 0.117, respectively (58). Many of these changes have the potential to substantially improve the QoL of patients and their carers.

7.2.1 Patients

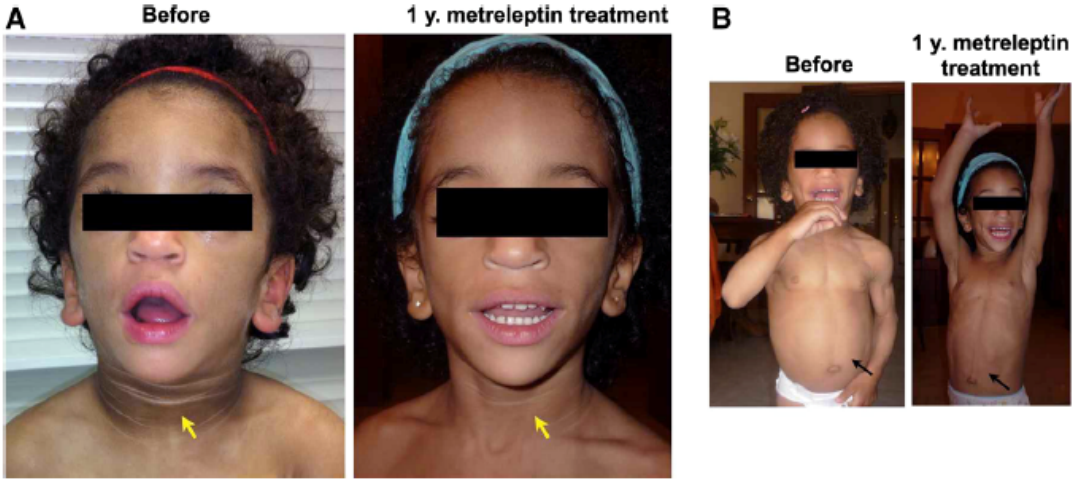
7.2.1.1 Improvements in emotional well-being

In the *Lipodystrophy Patient and Carer Survey*, patients who mentioned experiencing mental health disorders reported treatment with behavioural therapy and pharmaceutical drugs (8). However, as in this cohort of lipodystrophy patients mental health disorders usually stemmed from phenotypic expression of symptoms, improvements in physical appearance may be associated with reducing the emotional burden of burden of lipodystrophy by alleviating resulting symptoms of depression and low self-esteem. Improvements in the physical appearance of lipodystrophy patients have been noted after metreleptin, including improvements in facial fat deposition, improvements in acanthosis nigricans and having a less prominent abdomen and decreased girth (Figure 8) (32,59,60).

Some patients also reported a positive effect of leptin on their general outlook in day to day mood and life (8).

> *"…since I started the Leptin, it's made such a big difference, like the way I feel but then also seeing in my blood work and in my blood sugars, how much everything's changed, it kind of just makes you feel like – it gives you back that positivity that you kind of lost before."*

Figure 8: Effect of metreleptin on a young girl (age 23 months old) with regard to A) acanthosis nigricans and B) hepatic steatosis



Source: Araujo-Vilar, 2015 (59)

7.2.1.2 Improvements in physical health

Metreleptin has been shown to improve metabolic status such as high triglyceride and HbA1c levels unresponsive to other treatments. In the NIH studies 991265/20010769 (17), clinically meaningful and statistically significant improvements in HbA1c 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 corresponding to indicated PL population for metreleptin. HbA1c reductions of this magnitude are associated with significant reductions in clinical complications associated with hyperglycaemia; results of the UK Prospective Diabetes Study (UKPDS) conducted in over 4,500 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 MI, and 37% reduction in risk for microvascular complications (61,62). By extension, the HbA1c reductions achieved by metreleptin treatment reduce the risk of the micro and macrovascular complications associated with diabetes, thereby improving the QoL of patients.

In the *Lipodystrophy Patient and Carer Survey*, four patients mentioned reduced usage of insulin to control their blood glucose levels subsequent to metreleptin treatment, leading to a reduced utilization of healthcare resources (8). This is reflected through 41% of patients being able to stop insulin in NIH studies 991265/20010769 (17).

> *"Not to stay over, but yes, I was in there for I do have to go – prior to leptin, I was in various appointment systems several times a week. But once I was diagnosed with lipodystrophy and then got the leptin because everything started to work properly, I mean, I just go once every three to six months now to the various consultants I see.*

But now [after initiating leptin therapy], it's like probably once or twice probably every six months, which is way, way better. Way, way better. I used to be at the hospital all the time, and I would spend days at the hospital."

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). These improvements in triglyceride levels are likely to reduce the risk of developing cardiovascular disease and pancreatitis (63). Furthermore, the efficacy of metreleptin is demonstrated as episodes of pancreatitis arising when treatment with metreleptin is discontinued (17).

The improvements in HbA1c and triglyceride levels occurred in some patients despite reductions in or even discontinuation of the use of antidiabetic (including insulin, orally administered agents, or both) and/or lipid lowering therapies. Furthermore, despite excessive doses of insulin, glycaemic targets are rarely achieved without metreleptin therapy: mean HbA1c was 8.4% in patients with generalised lipodystrophy, and 8.1% in those with partial lipodystrophy when managed with insulin therapy alone. After metreleptin treatment, patients with generalised lipodystrophy frequently achieved glycaemic targets (with a mean HbA1c 6.4%) and reduced their mean insulin dose by an average 103 units per day (with total discontinuation of insulin achieved in many patients). After metreleptin treatment, patients with partial lipodystrophy were closer to achieving glycaemic targets (mean HbA1c 7.3%). (17,64) This suggests metreleptin offers the potential to reduce the burden of diabetes and/or hypertriglyceridaemia management itself, on both the patient (e.g. reducing pill burden) and the health service.

Metreleptin is also associated with improvements in lipodystrophy associated liver disease. Significant improvements in steatosis, ballooning injury and non-alcoholic steatohepatitis (NASH) scores have been reported as a result of metreleptin (9,12,36,41,42). NASH, a frequent condition in lipodystrophy patients, is commonly associated with elevated measurements of liver function, such as ALT, AST and liver volume. Thus, these markers are useful surrogates for NASH. Accordingly, metreleptin is associated with reductions in ALT, AST and liver volume (9,12,36,38,39).

7.2.1.3 Carers

The reduced healthcare burden on patients as a result of metreleptin use may ultimately reduce carer burden. The *Lipodystrophy Caregiver Burden Survey* reported that carers spent a substantial amount of time accompanying patients to medical appointments (12):

"… Hospital appointments, mental health issues, long term planning, medication…"

"… Taking him to hospital appointments, overseeing test results, general support but none that are physical…"

Carers also expressed concerns about the future of lipodystrophy drugs, including metreleptin (12). Secure availability of metreleptin may alleviate these anxieties, ultimately improving quality of life for both patients and carers.

"…Her medication (leptin) has been threatened and if this could be resolved that would make my job easier as it has made a huge difference to her health -it has been a wonder drug -it controlled her diabetes and lipid levels and we both worry hugely about what impact it would have if it were taken away"

"…I know that the treatment is paid for […] but I am concerned about this in the future due to NICE guidelines. Leptin helps her and is still funded but this may dry up in the future -this could be a worry financially"

Overall, metreleptin is anticipated to mitigate the clinical and QoL impact, as well alleviating the burden to the NHS associated with lipodystrophy patients' metabolic disorders, progressive organ damage, physical appearance, hyperphagia, female reproductive dysfunction, and depression.

8 Extent and nature of current treatment options

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 recommendation for their treatment.

Metreleptin has not been launched in the UK (see Section 3.4) and there are no other licenced treatments available for patients with lipodystrophy. The current mainstay for the management of lipodystrophy is diet and lifestyle modification. The metabolic complications associated with lipodystrophy are currently managed in the NHS in England via the additional use of a combination of supportive care therapies, such as lipid-lowering and anti-hyperglycaemic therapies. Throughout the submission, the term 'supportive care' refers to the use of these therapies.

The introduction of metreleptin is expected to displace or reduce the use of supportive care in lipodystrophy patients.

There is an EAP currently available via the Addenbrooke's centre prior to the launch of metreleptin. This is described further in Section 8.1.1 below.

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

NHS England established a service specification in 2013 (A03/S(HSS)/b) (29). The service is targeted at patients with lipodystrophy 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 Early Access Programme (EAP), treatment with metreleptin in England is currently provided at this centre for patients with GL and PL prior to launch, where the service specification (A03/S(HSS)/b) is 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 lipodystrophy is shown in Table 9.

Table 9: Overview of the NHS service specification for patients with lipodystrophy

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 lipodystrophy/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 lipodystrophy 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 lipodystrophy 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; NHS, National Health Service; rh, recombinant human	

Source: NHS England (A03/S(HSS)/b) (29)

International expert guidelines

8.1.1.1 Diagnosis

Due to the rarity of lipodystrophy, which is classed as an ultra-rare disease, many clinicians are unfamiliar with its diagnosis and management. No firm diagnostic criteria for lipodystrophy have been established, owing, in part, to difficulty in diagnosing the disease and distinguishing between sub-types (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 of lipodystrophy (2,5). In addition, Araújo-Vilar and Santini (35) has recently published a step-by-step approach to the diagnosis of lipodystrophy.

There are multiple difficulties in diagnosing lipodystrophy. Firstly, recognising the loss of subcutaneous fat is particularly challenging in PL, and especially in men in whom low body fat can occur naturally (2). Secondly, in both congenital and acquired lipodystrophy, the loss of subcutaneous adipose tissue may be gradual and thus delaying diagnosis.

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

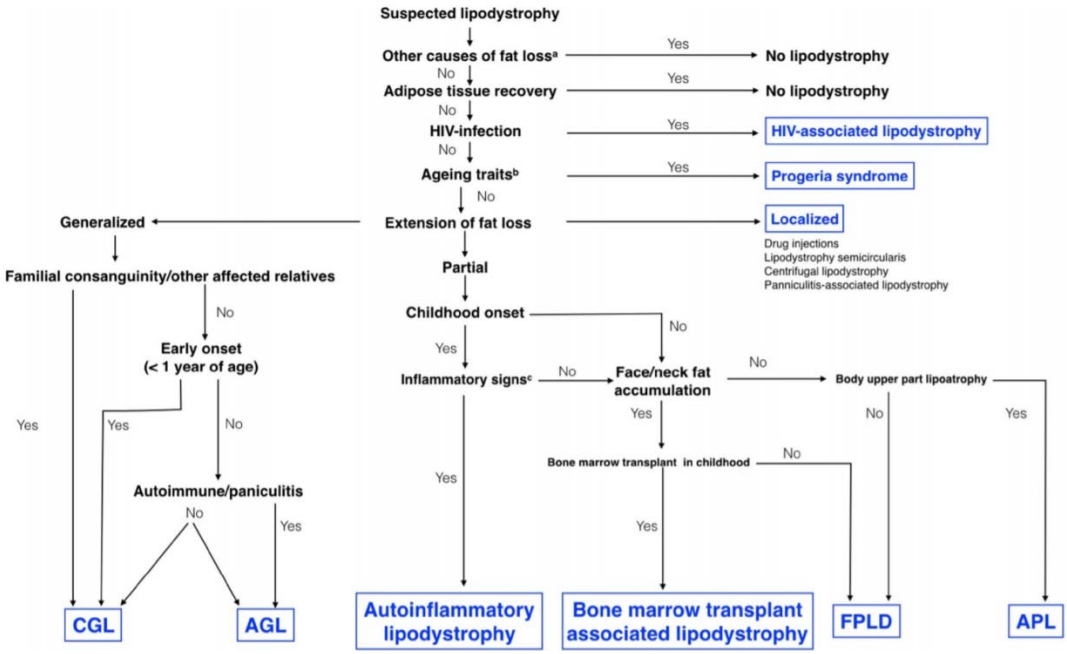
Differentiation of genetic and acquired lipodystrophy can be hampered by the heterogeneity of subcutaneous adipose tissue loss between lipodystrophy types. With CGL, patients typically have a lack of subcutaneous adipose tissue from infancy, whereas adipose tissue may appear as normal in infancy in patients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

In patients where there is a suspicion of lipodystrophy, Brown *et al* recommend screening for comorbidities associated with the disease including diabetes, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and cardiovascular and reproductive dysfunction (2).

The AACE have conducted a MEDLINE literature search and panel discussion to try and reach consensus on recommendations for lipodystrophy 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 lipodystrophy centre (5). Araújo-Vilar and Santini (35) summarises how clinicians can differentiate lipodystrophy from other diseases and determine the appropriate subtype using the following flow diagram (Figure 9).

Figure 9: A guide to diagnosing different subtypes of lipodystrophy



Source: Araújo-Vilar, (2019) (35)

8.1.1.2 Management

The consensus statement from the AACE on the clinical approach to the detection of lipodystrophy also includes a section on potential management modalities (5).The AACE suggest diet and exercise as options for the metabolic management of lipodystrophy alongside conventional anti-hyperglycaemic 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 lipodystrophy 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 lipodystrophy syndromes by Brown *et al.* recommends diet for managing the metabolic complications of lipodystrophy - however they recognise that studies of specific diets in lipodystrophy 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 lipodystrophy (5). 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).

Recommended additional treatments for the specific co-morbidities are outlined in Table 10.

Table 10: Additional Treatments for specific comorbidities

Co-morbid condition arising as a result of lipodystrophy	Management
Diabetes	Metformin is a first-line agent for diabetes and insulin resistance, approved for use in children above 10 years. Insulin is effective for hyperglycaemia (no restriction on age). In some patients, concentrated preparations and high doses may be required. Thiazolidinediones may improve metabolic complications (in adults) with 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 (adults only). 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 (adults only).
Hypertension	Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first-line treatments for hypertension in patients with diabetes (adults only).
Liver disease	In NAFLD not associated with lipodystrophy, 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 lipodystrophy and are not approved for NAFLD.
Cosmetic treatment	Patients should be assessed for distress related to lipodystrophy and referred as necessary to mental health professionals and/or plastic surgeons.
Abbreviations: GL, generalised lipodystrophy; NAFLD, non-alcoholic fatty liver disease; 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 ultra-rare nature of lipodystrophy, many clinicians are unfamiliar with diagnosis and management, and diagnosis can take many years. As such, patients can go through multiple healthcare checks before final diagnosis, leaving the underlying cause of their disease unmanaged and the disease progressing.

Most new cases of lipodystrophy in England are identified most commonly by diabetes specialists, endocrinologists and lipid specialists. Patients may be referred onto the only specialist centre in the UK (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 also provided at this centre through an EAP (See Section 3.4).

Conventional therapeutic options include lifestyle modifications (diet and exercise), and anti-hyperglycaemic and lipid-lowering medications. Based on UK clinical opinion, patients are usually reviewed in the clinic every 6 to 12 months if receiving standard of care and every 6 months if receiving metreleptin. This is in line with the service specification (Section 8.1.1). Patients are usually reviewed by their local team and/or GP between appointments at the specialist centre.

The disease's heterogeneity means the clinical pathway of care can vary between patients with lipodystrophy in England. Management of patients with lipodystrophy is complex and gold standard management of lipodystrophy requires a multidisciplinary team including 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 (anti-hyperglycaemic treatments, such as metformin) and hypertriglyceridaemia (fibrates, statins). Despite availability of these therapies, combinations of drugs, including very high doses of insulin, are ineffective and do not achieve adequate diabetes control in many patients with lipodystrophy. The doses of insulin used are beyond what is typically used and are simply impractical in most clinical contexts (13). Cosmetic treatment may be required to improve physical appearance, however patients in England may have problems gaining funding for such procedures through the NHS and they may need to seek private treatment which can present a personal financial burden. Anti-androgens may be required for PCOS and hyperandrogenism. Other services that may be required include referral to a dermatologist for severe acanthosis nigricans and/or skin tags and referral to fertility services (67).

As described, metreleptin has been available at Addenbrooke's Hospital via an EAP. A NICE recommendation provides an opportunity to continue treatment in patients with lipodystrophy, in whom metreleptin can address, and is currently addressing, the underlying cause of their condition. It also fulfils an unmet need

for PL patients who are not effectively controlled on standard of care therapy alone.

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

Outside of the EAP operating at Addenbrooke's Hospital, patients are only managed with treatments that address the signs and symptoms of the disease. Metreleptin is the only licensed treatment available to treat the underlying cause of lipodystrophy, i.e., leptin deficiency. Lipodystrophy is a multi-factorial disease with numerous consequences stemming from the inability to store fats in adipose tissue and leptin deficiency. As such these patients are at risk of developing progressive organ abnormalities in multiple organs, as well as suffering a negative impact on their quality of life and wellbeing. Interventions, such as metreleptin, which can slow the disease should be started as soon as possible in generalised lipodystrophy patients to treat metabolic and endocrine abnormalities, and prevent these comorbidities in children (2).

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

Consultants at Addenbrooke's CUH recommend that the pathway of care for metreleptin will continue in a manner that is consistent with the EAP. It is expected that metreleptin treatment initiation will be available via specialists centres only, such as Addenbrooke's Hospital and managed via the NHS service specification for patients with lipodystrophy.

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.

Metreleptin, a recombinant analogue of the human hormone leptin, is the first and only licensed treatment to specifically target the underlying cause of lipodystrophy (leptin deficiency). Metreleptin therapy is effective at reducing HbA1c, triglycerides, liver volume and the incidence of pancreatitis. By restoring leptin and its associated metabolic function therein, metreleptin can halt/slow disease progression and organ damage. Metreleptin therapy was found to be associated with a statistically-significant reduction in the risk of progression from 2 to 3 and from 3 to 4 abnormalities, of approximately 50% (50). As such, metreleptin may extend the survival of patients and significantly improve patient and carer quality of life. Patients have had access to metreleptin free of charge via the EAP at Addenbrooke's Hospital, for more than 10 years (see Section 3.4 and 9.6).

The metabolic abnormalities associated with lipodystrophy are often severe, and conventional treatments, alone or in combination, are likely to be inadequate at re-establishing metabolic control. An example of this inadequacy is the use of lifestyle modifications as therapy. Diet therapy aims to improve metabolic abnormalities via the reduction of triglycerides and glucose. However, leptin deficiency causes hyperphagia, a key mechanism of the disease, which makes adherence to diet therapy impossible for many patients and is therefore not appropriate for the treatment of lipodystrophy (13).

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

Based on the positive patient and clinician experience of metreleptin treatment for lipodystrophy via the EAP at Addenbrookes and Specialist service, no changes to the way current services are organised or delivered are anticipated with the introduction of reimbursed metreleptin.

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.
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. Patients and/or carers should prepare and administer the first dose of the medicinal product under the supervision of a qualified healthcare professional. A regular review of the patient's self-administration technique is recommended (up to quarterly) as indicated by their clinical progress whilst taking metreleptin (29).

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.

As metreleptin is administered by the patient or their carer at home at a location of their choice after treatment initiation in a specialist centre, no additional facilities, technologies or infrastructure are 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 with metreleptin treatment.

Symptomatic therapies, including interventions relating to diabetes, may be reduced or stopped completely. In NIH studies 991265/200110769 among the 39 patients with GL who were receiving insulin at baseline, 16 (41%) were able to discontinue insulin use altogether after starting metreleptin. Most of these patients (13 of 16) were able to stop insulin use within the first year of metreleptin. For the 32 patients with GL who were receiving oral anti-diabetic medicinal products at baseline, 7 (22%) were able to discontinue their use. A total of 8 (24%) of the 34 patients with GL who were receiving lipid-lowering therapies at baseline discontinued their use during metreleptin treatment (21).

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 *de novo* systematic literature review (SLR) was conducted in EMBASE, Medline and Medline® In-Process to identify relevant clinical studies for metreleptin and the comparator (standard of care), which addresses the key concerns raised by the ERG (68) and NICE (1) regarding the searches that were run as part of previous submission proceedings. The key concerns raised and how these have been addressed are summarised in Table 11.

Table 11: Key changes in the de novo clinical SLR approach taken to address previous concerns raised by NICE and / or the ERF

NICE and / or ERG concerns about previous clinical SLRs	How this has been addressed in the de novo SLR for EMBASE, Medline and Medline® In-Process database searches
• "*…because of limitations in the search strategy and exclusion criteria, relevant comparator or natural history studies could have been missed*" (section 4.4, FED (1)). • "*The search strategies did not include any search terms for comparators*" (ERG Report) (68).	• New search strategy developed, including terms added in for comparators in line with the NICE final scope • Validated interventional SIGN (SIGN.ac.uk) and ERG natural history search filters used • *De novo* inclusion and exclusion criteria employed (see Section 9.2.1)

Search terms for interventions were "u*nnecessarily exploded*" and "*additional terms for the condition … could have been added to the strategies to increase sensitivity*" (ERG Report) (68).	New search strategy uses MeSH descriptor terms with relevant synonyms and ERG population filters

Abbreviations: ERG – Evidence Review Group; FED – Final evaluation determination; SLR – Systematic literature review

The search of the Cochrane Central Register of Controlled Trials from the previous SLR was updated to identify any new relevant publications. Full details of the search are provided in Appendix 1 (section 17.1).

The SLR also included HRQL, cost and resource use, and economic evidence, which is reported in Section 10.1.5 and Section 11.

Unpublished studies

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

Sources of unpublished clinical data relevant to this appraisal were identified from internal data and information on file at Amryt and are included in this submission.

9.2 Study selection

9.2.1 Complete table C1 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.

The inclusion and exclusion criteria used in the SLR are outlined in Appendix 1, Table 60.

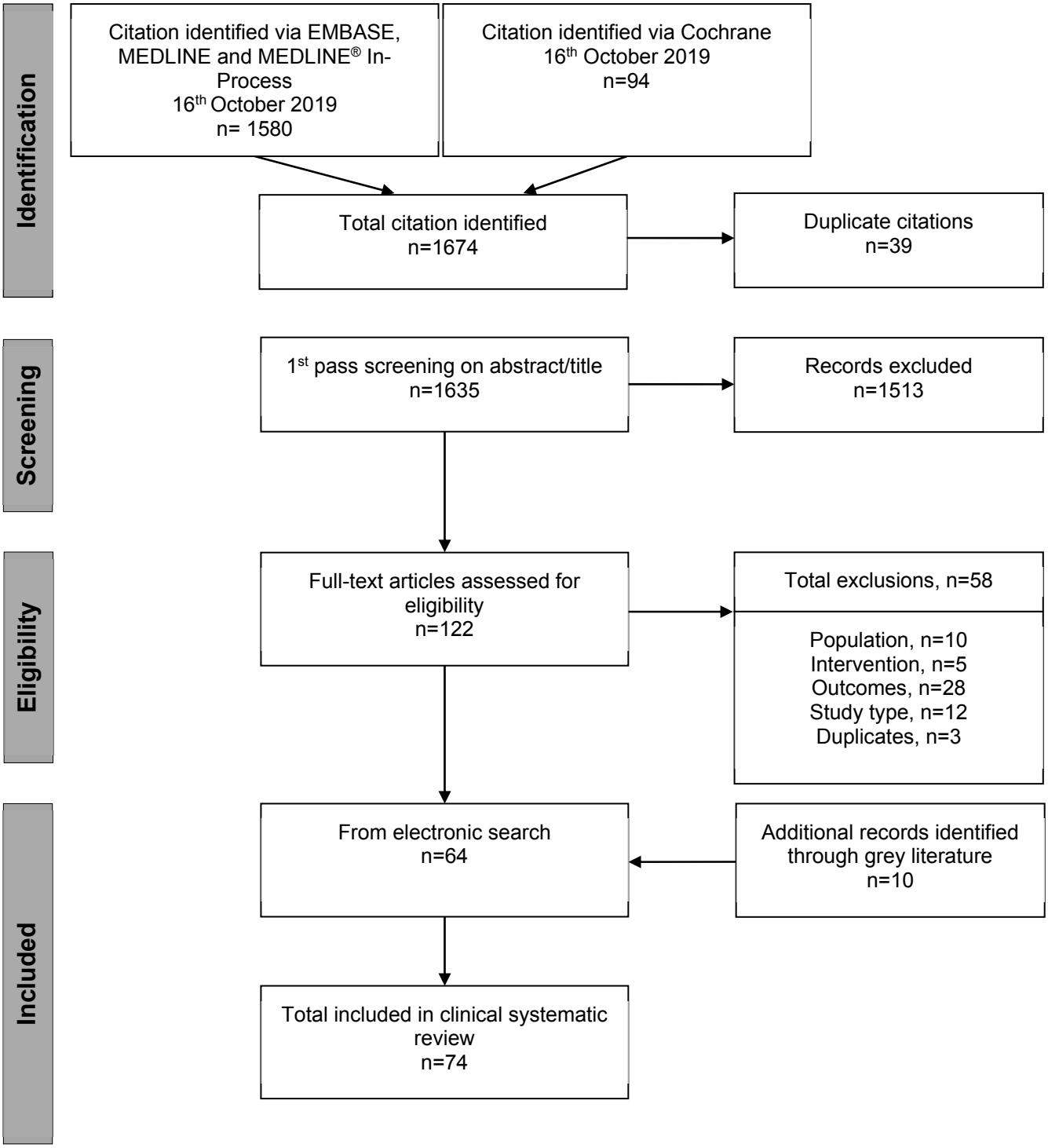
9.2.2 **Report the numbers of published studies included and excluded at each stage in an appropriate format.**

Of the 1,635 titles and abstracts screened against the inclusion criteria for clinical studies, 1,513 references did not meet the criteria and were excluded. The full texts of the remaining 122 clinical references were retrieved and reviewed against the selection criteria. Of these, 58 were excluded: 28 did not report data on the relevant outcomes, 12 did not meet the study type inclusion criteria, 10 did not contain the relevant population, 5 did not include the relevant intervention and 3 were duplicates. This meant that 64 references were included, with an additional ten references provided from or identified through

the grey literature search, giving a total of 74 references that met the selection criteria for the clinical SLR (Figure 4).

The previous SLRs conducted previously originally found a total of 46 references (27 references from the original SLR and an additional 19 references from the updated SLR). The previously identified references identified were reviewed against the selection criteria in Table 61. 28 of 46 references are included in this de novo SLR. Section 17.1 (Appendix 1) includes a table summarises which of these studies were excluded with reasons (Table 61). Table 62 also summarises all the studies which reached second pass and were excluded in this de novo SLR.

Figure 10: Schematic for the clinical SLR



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.

Table 60 in Section 17.1 (Appendix 1) describes the inclusion and exclusion criteria used in the SLR 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.

The literature search for unpublished studies identified clinical study reports (CSRs) for the National Institute of Health (NIH) NIH 991265/20010769 and FHA101 studies. In addition, the technical report for the NIH follow-up study, was identified.

9.3 Complete list of relevant studies

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables C1 and C2.

The details of all 74 published references are detailed in Appendix 6: List of studies, tables Table 68–Table 84. There were 38 observational references which evaluated metreleptin as an intervention, covering 12 clinical studies, 35 observational references which did not include metreleptin as an intervention, and one randomised controlled trial (RCT) which compared Cholic Acid therapy with placebo. There were no references identified which compared metreleptin to standard of care alone.

The relevant metreleptin studies identified were NIH 991265/20010769, NIH follow-up and FHA101, both of which had a single-arm design. Details of these studies have been provided in

Table 12 and Table 13 below.

- **NIH studies 991265/20010769** - This was an open-label, single-arm, investigator-led study conducted by the NIH in the US. The study was sponsored by Aegerion Pharmaceuticals, Inc., the company who acquired metreleptin in 2015 and submitted its licensing application in Europe for metreleptin as a treatment for GL and with severe PL in December 2016; The study had been ongoing from 2000-2014, with continuous enrolment and variable duration of follow-up through that period. The study integrates long-term safety and efficacy data from two related investigator-initiated studies (NIH991265 and NIH20010769) conducted the NIH involving metreleptin administration in patients CGL, AGL, APL or FPL. Although conducted separately, these two studies can be considered a single study since they employed a similar protocol and eight out of nine patients studied under the pilot open-label study NIH991265 continued treatment in the long-term open label study NIH20010769. Thus, it was deemed appropriate to integrate the two studies into one analysis to allow for a robust evaluation of the safety and efficacy of metreleptin treatment in this orphan population. The primary source of evidence is the CSR; the latest 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. 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 (

- Table 12).

- **NIH follow-up** - The NIH follow-up study extended the 991265/20010769 study by undertaking a chart review to collect long-term data from 112 patients with lipodystrophy who received metreleptin therapy at the NIH. Of the 112 patients included in the follow-up study, 105 patients were part of the original studies (991265/20010769) (16). The data from this study are available via unpublished sources only.

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

Table 12: List of relevant published studies

Primary study reference	Study name (acronym)	Other references identified	Population	Intervention
CSR (17)	NIH 991265/20010769 (NCT00025883)	Oral *et al.* 2002(69) Javor *et al.* 2005(32) Park *et al*. 2007(70) Abel *et al.* 2016(71) Brown *et al.* 2017(72) Brown *et al.* 2018(20) Chong *et al.* 2010(73) Diker-Cohen *et al*. 2015(74) Kassai *et al.* 2016(75) Lee *et al*. 2019(49) Muniyappa *et al*. 2014(76) Muniyappa *et al*. 2017(77) Oral *et al.* 2017(46) Oral *et al.* 2017(78) Sekizkardes *et al*. 2019(79)	Patients with GL or PL	Metreleptin
CSR (66)	FHA101 (NCT00677313)	Zadeh *et al.* 2013(65)	Patients with GL or PL	Metreleptin

Table 13: List of relevant unpublished studies

Data source	Study name (acronym)	Other references identified	Population	Intervention
Tuttle *et al.* 2018 *Technical Report*	NIH follow-up		Patients with GL or PL	Metreleptin

9.3.2 State the rationale behind excluding any of the published studies listed in tables C3 and C4.

None of the studies listed in

Table 12 and Table 13 have been excluded.

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

Metreleptin received a marketing authorisation from the EMA based on the pivotal NIH studies 991265/200110769, initiated by the NIH in the US (27,80) (see Section 3.1). As such, this study is described in more detail below. In addition, supportive evidence is provided from the, expanded-access program, study FHA101 (81).

9.4.1.1 *NIH studies 991265/200110769*

NIH studies 991265/200110769 was an open-label, investigator-sponsored trial conducted at the NIH to examine whether treatment with metreleptin could improve the metabolic sequelae found in patients with lipodystrophy syndromes, including pathological derangements in glucose and lipid homeostasis (69,74,82). Patients were enrolled from the US, countries in Europe including the UK, and Eastern Mediterranean (17). Unlike a sponsor initiated Phase III clinical trial, the NIH pivotal studies 991265/200110769 faced the limitations of its open-label single arm design.

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 lipodystrophy (69,74,82). Utilising a placebo control in this patient population at risk for serious, life-threatening metabolic complications after marked improvements with metreleptin were demonstrated in Study NIH 991265 was considered not justifiable based on ethical considerations. In addition, the studies' efficacy endpoints are objective

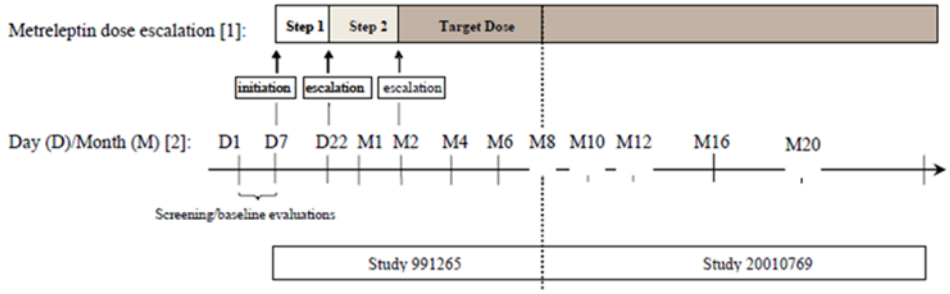
measurements, including HbA1c and triglycerides, and thus treatment effects could be appropriately evaluated with a single-arm (baseline-controlled, within patient) design (81).

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 has been 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 (17).

Figure 11 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 11: Study design for studies (a) NIH 991265 and (b) NIH 20010769

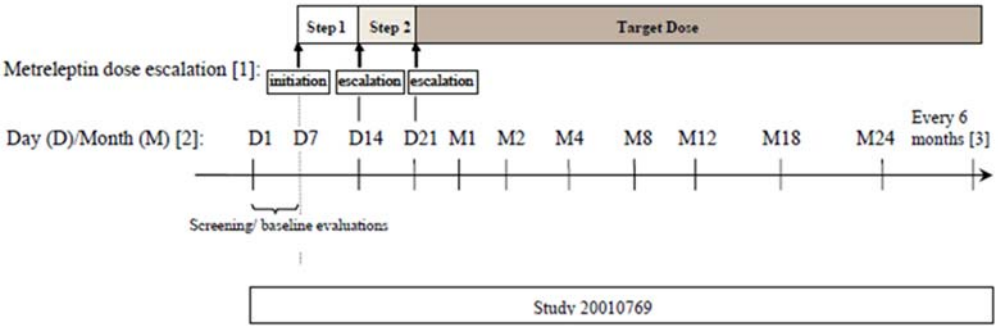
(a) NIH 991265



[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) NIH 20010769



[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: NIH studies 991265/20010769 CSR (17)

Patients self-administered (or had their caregiver administer) metreleptin via subcutaneous injection once or twice daily, in 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 (17).

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 (17).

A summary of the methodology is shown in Table 14.

Table 14: Summary of methodology for NIH studies 991265/200110769

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 lipodystrophy 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 • 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 >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 • Patients with acquired lipodystrophy and a haematologic abnormality such as neutropenia and/or lymphadenopathy (added as an amendment to Study 2001769 protocol)
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, Haemoglobin A1c; HDL-C, high density lipoprotein cholesterol; HIV, Human immunodeficiency virus; 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

*Region was missing for 3% of patients with GL

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

[b] Postprandially elevated triglyceride concentration formed part of inclusion criteria for study NIH 20010769 (but not NIH 991265)

Source: Oral. 2002,(69); Diker-Cohen, 2015, (74); Clinicaltrials.gov NCT00025883, (82); *Source: NIH studies 991265/20010769 CSR, (17)

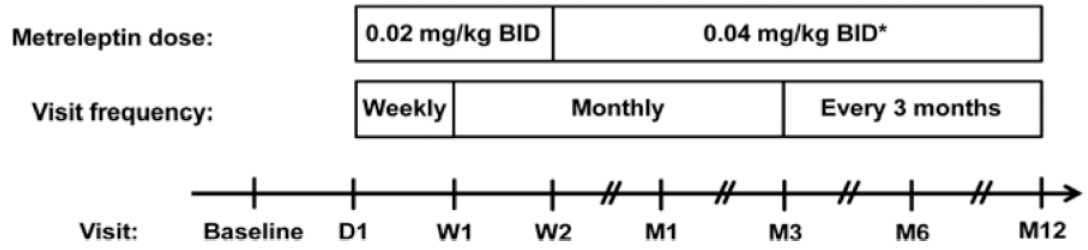
9.4.1.2 *Study FHA101*

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 lipodystrophy. The study was initiated in 2008 in the US and as with NIH studies 991265/200110769 as of December 2014, all patients were either off metreleptin treatment or had transitioned to commercial product or free-drug programmes. Patients were enrolled from the US (66).

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 12). 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 12: 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, (66)

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 15.

Table 15: Summary of methodology for study FHA101

Study name	FHA101
Objective	To provide expanded access to metreleptin to patients with lipodystrophy 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)[a]
Inclusion criteria	Male or female ≥5 years old Physician-confirmed lipodystrophy 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 lipodystrophy and clinically significant haematologic abnormalities (such as neutropenia and/or lymphadenopathy) Known infectious liver disease Known allergies to *E. coli*-derived proteins or hypersensitivity to any component of study treatment Was an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the

	study at the clinical study site, or is directly affiliated with the study at the clinical study site Prisoners or patients who were involuntarily incarcerated (added as an amendment) Patients who were compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness (added as an amendment)
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, Haemoglobin A1c; HDL-C, High density lipoprotein cholesterol; HIV, Human immunodeficiency virus; 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 (83); Ajluni, 2016 (60); *Study FHA101 CSR (66)

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).

Data from NIH studies 991265/200110769 were sourced from published sources (Oral 2002 (69), Diker-Cohen 2015 (74), Clinicaltrials.gov NCT00025883 (82); EPAR public assessment report (81)) and the clinical study report (17). Data from study FHA101 were also sourced from published sources (Ajluni 2016 (60), Clinicaltrials.gov NCT00677313 (83); EPAR public assessment report (81)) and clinical study report (Amyrt, data on file (66)).

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

Baseline characteristics for NIH studies 991265/200110769 and FHA101 are shown in **Error! Reference source not found.** and Table 15 respectively.

Baseline demographics

Among the 66 patients with GL in NIH studies 991265/200110769, 77% were female with Caucasians representing 47% of the population; in the PL subgroup, all but 1 of the 31 patients were female and the majority were Caucasian (84%) (Table 16) 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 16).

In NIH studies 991265/200110769 the median age of the GL group was 15 years with 68% of patients <18 years of age. The median age of the PL subgroup was 38 years, 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 lipodystrophy and clearly show that the PL subgroup, aligned to the SmPC, selected for evaluation of the effectiveness of metreleptin was similar, or in some measures less severe, compared to the group of patients with GL (Table 16 and Table 17). These metabolic abnormalities were present despite the high use of antidiabetic medications and lipid-lowering therapies, suggesting that conventional therapies alone are insufficient in patients with severe hypertriglyceridaemia or severe insulin resistance requiring high-dose insulin (13).

Table 16: Baseline characteristics for NIH studies 991265/200110769

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)
Lipodystrophy 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)	8.7 (3.6, 26.5)	8.8 (5.0, 20.4)	7.0 (2.7, 20.4)
Fasting triglycerides, mmol/L			
Median (range)	4.6 (0.6, 143.3)	5.5 (1.2, 109.5)	4.1 (1.1, 109.5)
≥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, Haemoglobin A1c; 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: NIH studies 991265/20010769 CSR (17)

Table 17: 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)	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)
Lipodystrophy 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 (%)	4 (44.4)	2 (28.6)	9 (28.1)
AST, >ULN, n (%)	4 (44.4)	0	5 (15.6)
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; HbA1c, Haemoglobin A1c; 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 (66)

In NIH studies 991265/200110769 median HbA1c at baseline was similar for patients with GL or PL (8.7% and 8.6%, respectively) (Table 16). 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 high in patients with GL or PL subgroup (4.6 mmol/L and 5.5 mmol/L, respectively), which is representative of severe hypertriglyceridaemia (84).

In general, the baseline metabolic abnormalities for patients in study FHA101, although abnormal, were not as elevated as those for patients in NIH studies 991265/200110769 (Table 16 and Table 17**Error! Reference source not found.**). 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.

Baseline co-morbidities and medication history

In NIH studies 991265/200110769 all 107 patients had at least one medical history event reported. The most commonly reported medical history events in GL patients were hypertriglyceridaemia (71%) and diabetes mellitus (70%). Other relevant medical history included hepatomegaly/hepatosplenomegaly (62%), NASH including steatohepatitis (52%), proteinuria (45%), hypertension (36%), insulin resistance (29%), pancreatitis (27%), hepatic steatosis (24%) and hirsutism (21%) (17).

Of the defined PL subgroup, 94% of these patients had a history of hypertriglyceridaemia and 84% had diabetes. Hepatic steatosis and pancreatitis were each reported in 39% of PL subgroup patients, 23% had polycystic ovaries and 26% had NASH including steatohepatitis (17).

The majority of patients in the GL group (80%) and PL subgroup (97%) were receiving antidiabetic medications at study entry (Table 14) 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 (17).

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 (66).

Methodology comparison

Both NIH studies 991265/200110769 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 NIH studies 991265/200110769 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 an investigational new drug (IND) study, only HbA1c, glucose, triglycerides, and liver function tests were evaluated for efficacy.

Exposure

In NIH studies 991265/200110769 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 of the study when the eligibility criteria were modified to increase eligible leptin levels (17).

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 and was lower in males (3.0 mg; 0.057 mg/kg) than females (4.7 mg; 0.099 mg/kg). For patients in the PL subgroup, the median weighted average daily dose over the study period (8.1 mg) was higher than the GL group influenced by the higher BMI in PL patients and the fact that almost all PL were females. When considering a mg/kg basis, the median weighted average daily dose of

0.119 mg/kg was only marginally higher than females in the GL group (all but 1 patient in the PL subgroup was female) (17).

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 (66).

Addenbrooke's Hospital early-access data

To supplement the two key studies, NIH studies 991265/200110769 and study FHA101, additional retrospective data analysis was performed on data from the Addenbrooke's Hospital early-access program. As described in Section 3.4, there has been an ongoing EAP at Addenbrooke's Hospital with patients initiated on metreleptin for free of charge. Data has been collected to evaluate the baseline characteristics and the metabolic changes observed in the patients initiated. During the study, there has been further understanding in patients with PL and therefore is not necessarily representative of the patients that will be initiated on metreleptin the future.

Baseline characteristics are similar to the key studies and also show that the PL subgroup selected for evaluation of the effectiveness of metreleptin was similar, or in some measures less severe, compared to the group of patients with GL (Table 18).

Table 18: Baseline characteristics for Early Access Programme data Addenbrooke's Hospital

Characteristic	GL (N = 10)	PL (N = 21)	
		PL subgroup[a] (N = 18)	Overall (N = 21)
Female, n (%)	7 (70.0)	16 (88.9)	19 (90.5)
Race n (%)			
Caucasian	4 (40.0)	16 (88.9)	19 (90.5)
Asian	5 (50.0)	1 (5.6)	1 (4.8)
Unknown	1 (10.0)	1 (5.6)	1 (4.8)
Age at diagnosis, median (range)[b]	1 (1, 21)	23 (1, 53)	34.5 (1, 53)
<18 years, n(%)	5 (71.4)	2 (28.6)	2 (20.0)
≥18 years, n(%)	2 (28.6)	5 (71.4)	8 (80.0)
Lipodystrophy type, n(%)			
Acquired	3 (30.0)	1 (5.6)	1 (4.8)
Congenital/Familial	7 (70.0)	17 (94.4)	20 (95.2)
BMI, kg/m^2, median (range)[b]	19.5 (13.4, 24.6)	24.9 (22.2, 28.8)	24.9 (22.2, 28.8)
HbA1c, %[b]			
Median (range)	9.1 (5.1, 13.5)	7.3 (6.2, 15.3)	7.1 (5.7, 15.3)
≥6.5, n (%)	8 (88.9)	16 (88.9)	17 (81.0)
≥8.0, n (%)	8 (88.9)	7 (38.9)	7 (33.3)
Fasting triglycerides, mmol/L[b]			
Median (range)	4.6 (1.7, 17.1)	3.4 (1.5, 26.5)	3.2 (1.1, 26.5)
≥2.26 mmol/L, n(%)	9 (90.0)	14 (82.4)	15 (75.0)
≥5.65 mmol/L, n(%)	5 (50.0)	2 (11.8)	2 (10.0)
Anti-diabetic medications at baseline, n (%)[b]	7 (70.0)	7 (100.0)	10 (100.0)
Triglyceride-lowering medications at baseline, n (%)[b]	2 (28.6)	1 (20.0)	1 (14.3)

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; 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

[b]Where data are available

Source: Combined data on file (85,86)

Section 17.7, Table 86 summarises organ damage (liver, heart, kidney and pancreatitis) and other complications for patients in the Addenbrooke's Hospital early-access program, reported at baseline (87).

Among all patients where data was available (20 patients), 100% had liver damage, 3 (33%) GL and 2 (18%) PL had heart damage, 4 (44%) GL and 1 (9%) PL had kidney damage, and 2 (22%) GL and 1 (9%) PL had pancreatitis at baseline (87).

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

The NIH studies 991265/200110769 and FHA101 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 (17,66).

NIH studies 991265/200110769 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 NIH studies 991265/200110769. 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 (17,66).

Pre-specified subgroup analyses were performed based on a number of baseline factors, including metabolic abnormalities, age, lipodystrophy 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 NIH studies 991265/200110769, where the sample size allows for comparison across most subgroups (Section 9.6). 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 (17,66).

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.

The Disposition of the 107 patients enrolled and treated in NIH studies 991265/200110769 is summarised in Table 19.

Table 19: Patient disposition in NIH studies 991265/200110769

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, Haemoglobin A1c; 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: NIH studies 991265/200110769 CSR (17)

Disposition of the 41 patients enrolled and treated in study FHA101 is summarised in Table 20.

Table 20: Patient disposition in 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, Haemoglobin A1c; 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 (66)

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 NIH studies 991265/200110769, all but 1 (>99%) of the 107 patients received 6 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 in this study. More than one-quarter of patients (28%, 30 patients), received more than 6 years of treatment with metreleptin with 13 (12%) on treatment for 10 years or more. The maximum duration of metreleptin was ~14 years. Approximately one-third of GL patients (35%) and patients in the PL subgroup (36%) discontinued treatment prior to the end of the study (Table 19). The only events leading to discontinuations of study treatment other than the deaths in GL patients were: peripheral T-cell lymphoma (PTCL) in 1 GL patient and increased blood triglycerides and inadequate diabetes mellitus control in 1 GL patient. The only event leading to discontinuation in the PL subgroup was hypoxic-ischaemic encephalopathy (1 patient in the PL subgroup died due to hypoxic-ischaemic encephalopathy; the event was assessed as unrelated to study treatment). The most common reason for discontinuation was patient noncompliance (5 GL patients, 8% and 6 PL subgroup patients, 19%) (17).

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; reasons for discontinuation were reported with 1 patient being physician decision and the other being patient withdrawal (Table 20).

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.

Critical appraisals of NIH studies 991265/200110769 and FHA101 using the Downs and Black checklist are shown in Section 17.8, Table 87 and Table 88, respectively (88).

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 studies 991265/20010769

A summary of the primary endpoints, key secondary endpoints, other secondary endpoints and other endpoints of relevance is shown in Table 21 and described in more detail below. Adverse events (AEs), including cases of pancreatitis and infections, are described in Section **Error! Reference source not found.**

Table 21: Outcomes from NIH studies 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 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**	61	29	39
	Mean (SD)	14.7 (25.66)	15.7 (26.42)	12.5 (23.35)
Month 12 value, LOCF	**n**	58	27	36
	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	-49.6, -25.2	-37.1, -4.6
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**	62	30	40
	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 N = 62	PL subgroup N = 30[a]	PL overall 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 baseline	**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, Haemoglobin A1c; 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

[c] 95% CI based on the 2-sided exact binomial proportions

Source: NIH studies 991265/200110769 CSR (17).

Co-primary efficacy endpoints: effect of metreleptin on change from baseline in HbA1c and percent change from baseline in triglycerides at Month 12/LOCF

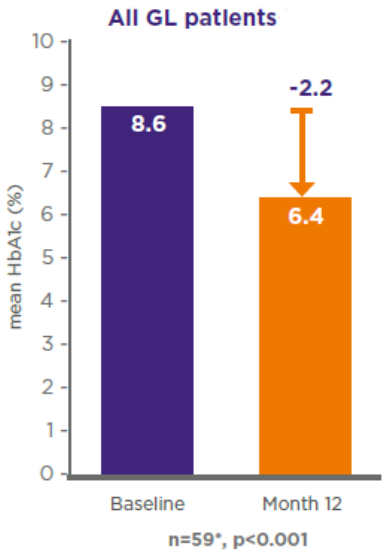
Treatment with metreleptin led to clinically meaningful and statistically significant improvements in glycaemic control and hypertriglyceridaemia in patients with GL and in the PL subgroup.

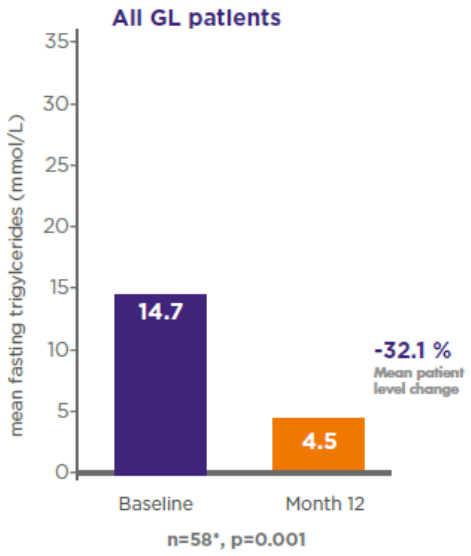
For GL patients, the changes from baseline to Month 12/LOCF were clinically meaningful and statistically significant for HbA1c, with a mean change of -2.2% ($p<0.001$), and for triglycerides, with a mean percent change of -32.1% ($p=0.001$) (Table 21,

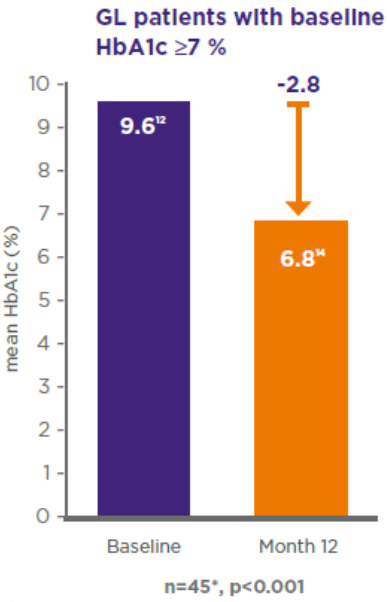
Figure 13). GL overall patients sustained clinically meaningful and statistically significant reductions in HbA1c and triglycerides at Month 12/LOCF. In addition GL patients with baseline HbA1c ≥7% and TG ≥5.65 mmol/L sustained clinically meaningful and statistically significant reductions in HbA1c and triglycerides at Month 12/LOCF, respectively (

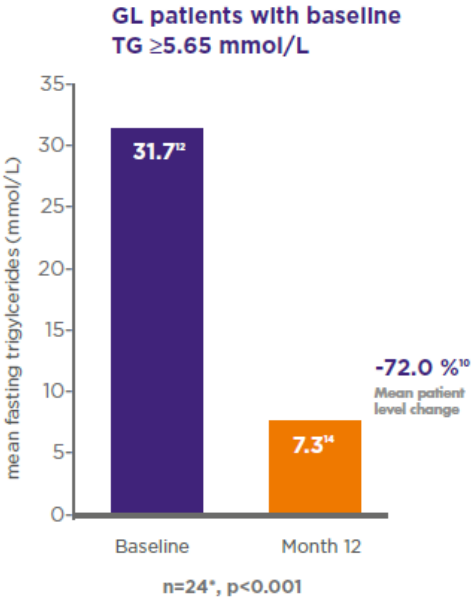
Figure 13) (17).

Figure 13: Mean change in HbA1c (%) and triglycerides (mmol/L) from baseline at month 12/LOCF in patients with GL treated with metreleptin in NIH studies 991265/20010769







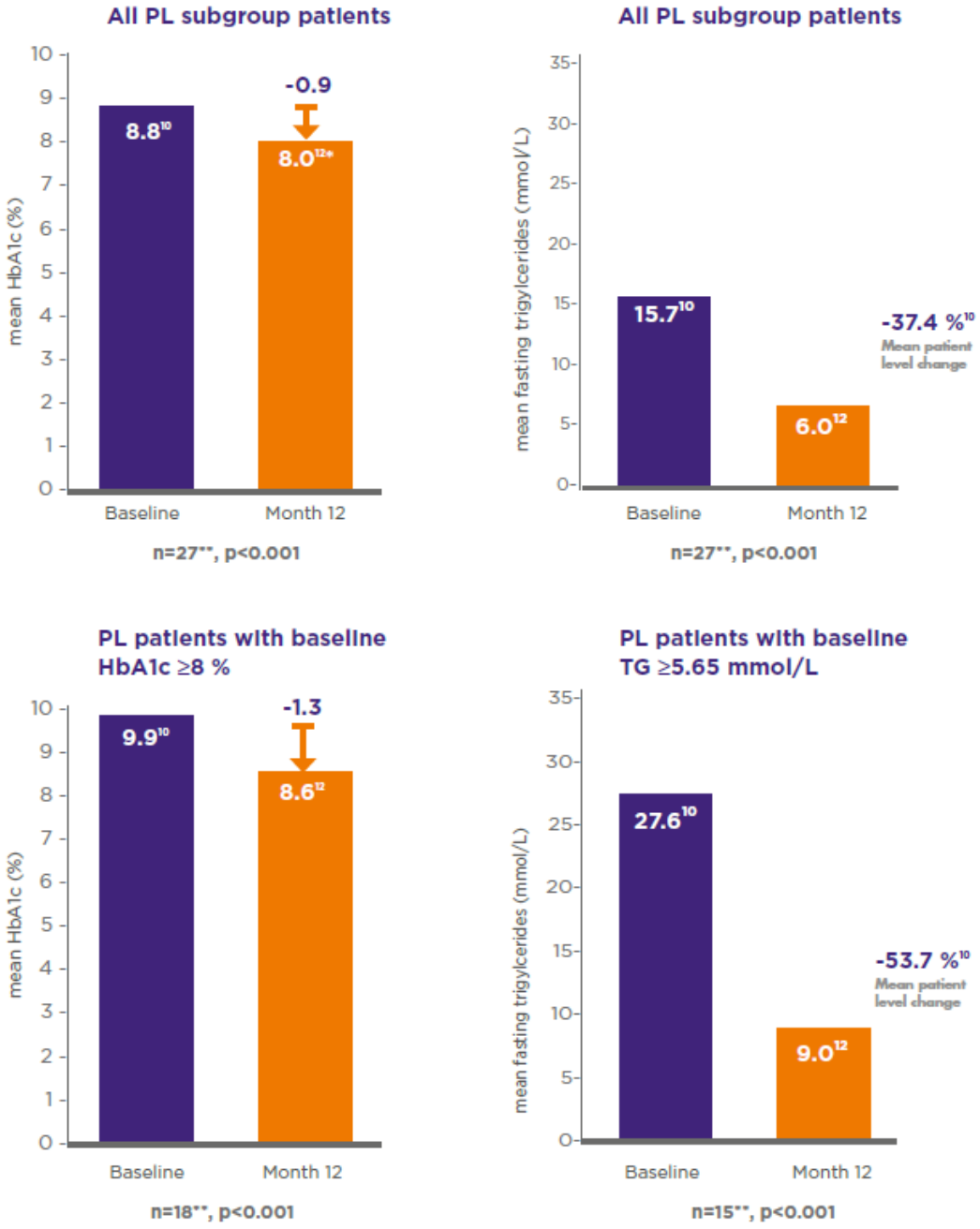


* n=number of patients with data at 12 months
Abbreviations: CI, Confidence interval; GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c.
Source: Myalepta: Specific solution product brochure (40), Metreleptin SmPC (21), Brown 2018 (20)

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, 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 Patient 901-080 who had a >1,000% increase in triglycerides to the primary endpoint; this was the only patient in the study with this level of

change at Month 12. This patient's study involvement was terminated 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 (Table 21,Figure 14) (17).

Figure 14: Mean change in HbA1c (%) and triglycerides (mmol/L) from baseline at month 12/LOCF in patients with PL treated with metreleptin in NIH studies 991265/20010769



Abbreviations: CI, Confidence interval; HbA1c, Haemoglobin A1c; PL, Partial lipodystrophy; TG, Triglycerides.
* rounding effect
** n=number of patients with data at 12 months
Source: Myalepta: Specific solution product brochure (40), Metreleptin SmPC (21) and NIH studies 991265/20010769 CSR (17)

Key secondary endpoint: Actual and percent change from baseline in fasting plasma glucose levels at Month 12/LOCF

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 21). 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 (17)**.**

Key secondary endpoint: Responder analysis – patients achieving target reductions in HbA1c and triglycerides at Month 12/LOCF

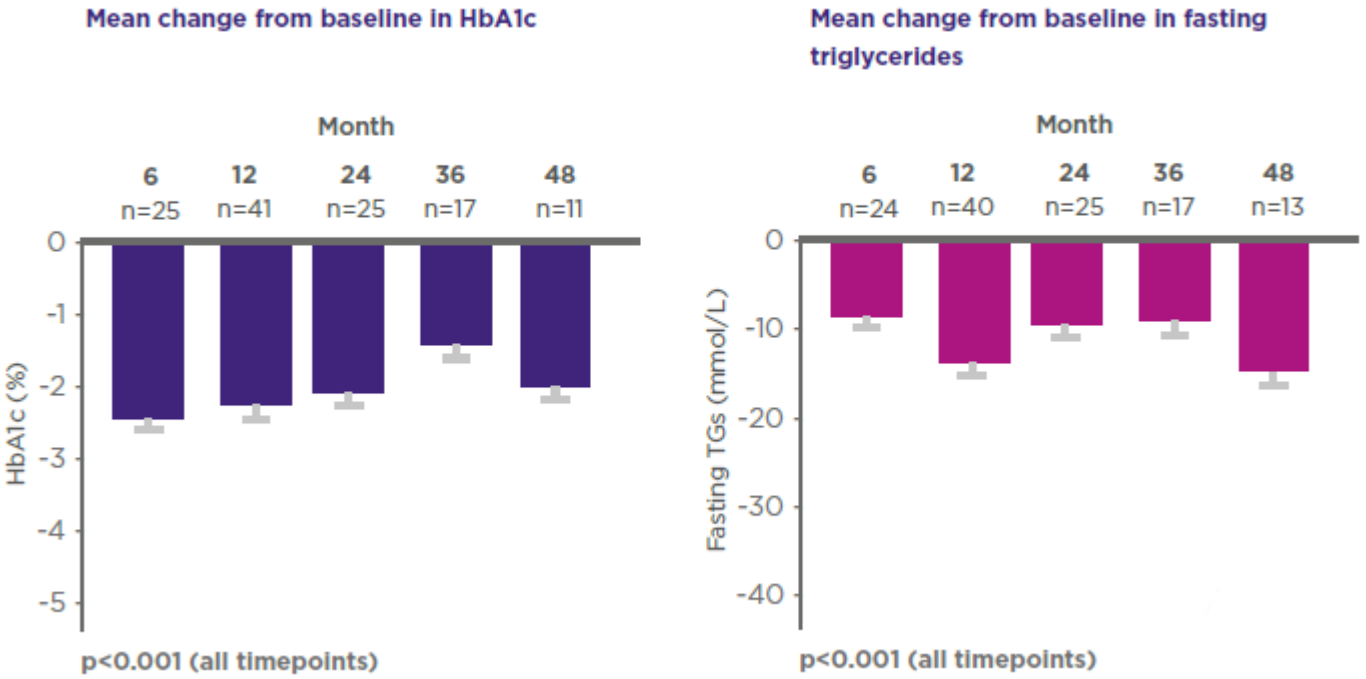
Nearly 80% of patients with GL achieved a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 66% achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides at that time. Results were consistent in the PL subgroup, with 68% of patients achieving 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 (17).

Other endpoints of relevance

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

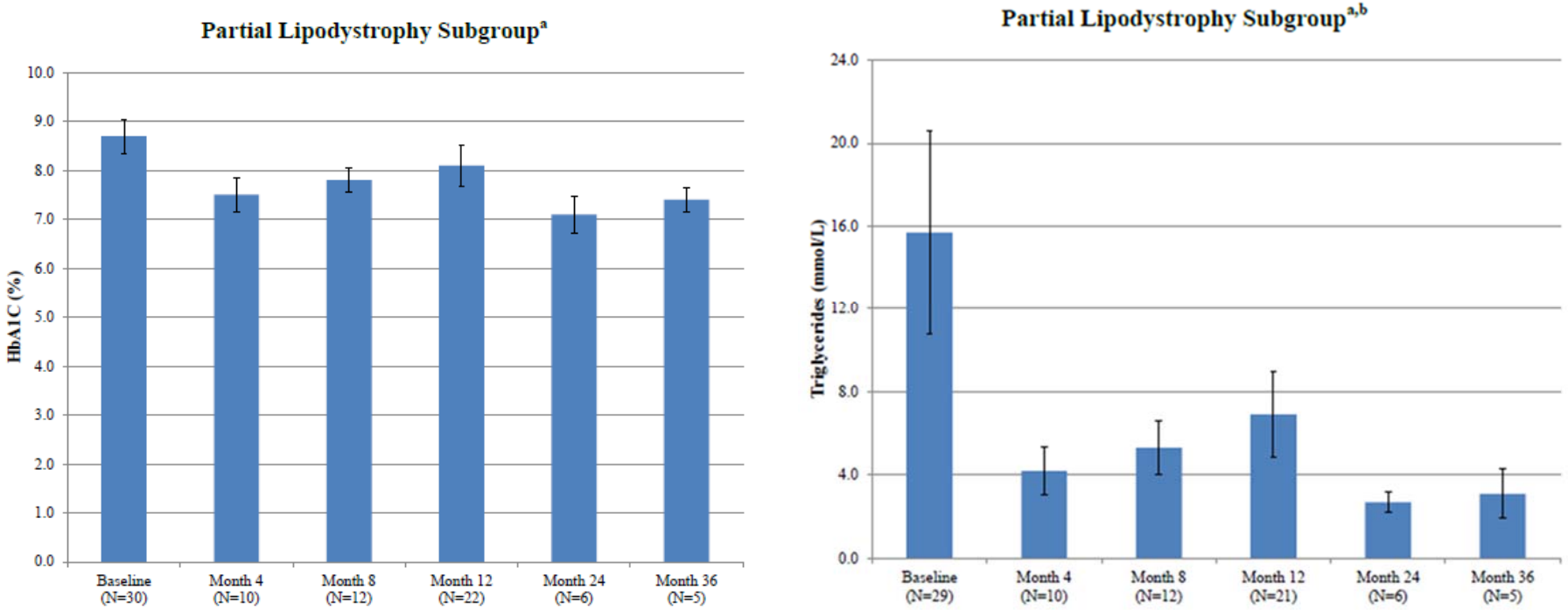
Long-term treatment with metreleptin led to clinically meaningful and statistically significant reductions in HbA1c and triglycerides in patients with GL and in the PL subgroup (17). Mean HbA1c and triglyceride levels through month 48 in GL patients and month 36 in PL subgroup patients are shown in Figure 15 and Figure 16.

Figure 15: Mean (SEM) change in HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24, 36 and 48 of metreleptin treatment in NIH studies 991265/20010769 in GL patients



Abbreviations: FAS, Full analysis set; HbA1c, Haemoglobin A1c; GL, Generalised lipodystrophy; SEM, Standard error of the mean.
Source: Myalepta: Specific solution product brochure (40) and Brown 2018 (20)

Figure 16: Mean (SEM) HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24 and 36 of metreleptin treatment (FAS population) in NIH studies 991265/20010769 in PL subgroup patients



Abbreviations: FAS, Full analysis set; 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: NIH studies 991265/20010769 CSR (17)

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. Importantly, the overall MMRM analysis, which evaluates average levels across all visits, showed a statistically significant decrease from baseline for GL patients, with an overall 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% ($p<0.001$) (17).

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% ($p=0.004$) (17).

Additionally, in the GL group, significant mean changes from baseline in HbA1c and triglyceride levels were reported for up to Month 48 with no loss of efficacy over time ($p < 0.001$ for both parameters) (20).

Change from baseline in fasting lipids at Month 12/LOCF

Changes in total cholesterol and LDL-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 21). 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 21) (17).

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. Substantial improvements in liver function tests and reductions in liver volume were noted in GL patients and in patients in the PL subgroup (17).

As noted in Table 16, 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 and AST versus baseline was -53.1 U/L and -23.8 U/L, respectively. 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 21). 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 (17).

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. 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% (17).

Results of paired liver biopsies from patients in NIH studies 991265/200110769 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. Patients with liver fibrosis at baseline remained stable on metreleptin (65).

Further exploratory analyses regarding the effect of metreleptin on: hyperphagia, concomitant medication use, growth and pubertal status are detailed in Section 17.9 (89).

In particular, with regards to hyperphagia, as published by Moran and colleagues from the NIH, metreleptin treatment of 14 patients with lipodystrophy (12 with GL and 2 with PL) significantly decreased food intake at 4 months from 3,170 kcal/day to 1,739 kcal/day (p=0.019) (89).

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, lipodystrophy subtype, and region. A summary of the key findings from the subgroup analyses are shown in Table 22.

Table 22: 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)
Lipodystrophy 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)

	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
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; HbA1c, Haemoglobin A1c; LOCF, Last observation carried forward; NA, Not-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 (NIH studies 991265/20010769, Listing 16.2.1.1)

	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
[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: NIH studies 991265/20010769 CSR (17)

Patients with worse metabolic abnormalities at baseline achieved greater mean decreases from baseline at Month 12/LOCF. Among 45 (72.6%) patients with GL who had a baseline HbA1c of ≥8% available at Month 12, the mean (SD) baseline HbA1c was 9.9% (1.48) and the mean reduction in HbA1c at Month 12 was -3.0%. Among 24 patients with GL who had a baseline triglyceride level ≥5.65 mmol/L 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 PL subgroup who had a baseline triglyceride level ≥5.65 mmol/L 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% (17).

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 (17).

9.6.1.2 *Study FHA101: supportive evidence*

The efficacy results in the supportive study FHA101 were, in general, consistent with those reported for Study NIH 991265/20010769, although the number of patients included in FHA101 were smaller and comprised of a greater proportion of PL patients. A detailed breakdown of the results is shown in Section 17.11, Table 90 and is summarised briefly here.

Co-primary efficacy endpoints: effect of metreleptin on change from baseline in HbA1c and percent change from baseline in triglycerides at Month 12/LOCF.

Among patients with GL, mean change from baseline to Month 12/LOCF for HbA1c was not statistically significant (-1.2%, p=0.360) and the mean percent change in triglycerides was not statistically significant (-26.9%, p=0.486) likely due to the small sample size for GL patients (n= 9 at baseline) (66). Among the 7 patients in the PL subgroup, mean change in HbA1c from baseline to Month 12/LOCF was not statistically significant (-0.8%, p=0.289) with the mean percent change in triglycerides was not statistically significant (-8.5%, p=0.485). 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 in triglycerides ranging from -5.7% to -52.3% from baseline to Month 12/LOCF (66).

Key secondary endpoint of relevance: Responder analysis – patients achieving target reductions in HbA1c and triglycerides at Month 12/LOCF.

Five patients (3 GL and 2 PL subgroup) had a ≥1.5% actual decrease in HbA1c or a ≥35% decrease in triglycerides at Month 12/LOCF (66). Of which, four patients (3 GL and 1 PL subgroup) achieved the highest target decreases of ≥2% in HbA1c or ≥40% in triglycerides (66).

Other secondary endpoints of relevance: analysis of change over time in HbA1c and triglycerides - persistence of efficacy.

Among patients with GL, LS mean changes in HbA1c and triglycerides based on the MMRM analysis were statistically significant for HbA1c only, with values of -0.7% (p=0.047) and -23.3% (p=0.059) respectively. Among patients in the PL subgroup, LS mean changes in HbA1c and triglycerides based on the MMRM analysis were statistically significant for HbA1c only, with values of -0.9% (p=0.011) and -4.3% (p=0.703) respectively (66).

Data from Addenbrooke's Hospital Early Access Programme: supportive evidence

Data were retrospectively obtained from Addenbrooke's Hospital on all patients included in the expanded access program since its initiation, up to date as of January 2020.

Exploratory analysis: change from baseline in HbA1c and triglycerides

Treatment with metreleptin led to long-term clinically meaningful improvements in glycaemic control and hypertriglyceridaemia in patients with GL and in the PL subgroup (Table 23). Among patients with GL, the mean actual change for HbA1c from baseline to Month 12 was -1.5% and the mean percent change in triglycerides was -48.4%. Among patients in the PL subgroup, the mean actual change for HbA1c from baseline to Month 12 was -1.1% and the mean percent change for triglycerides was -30.8%.

Changes continued to be sustained in the long term, up to 36 months (Table 23). Among patients with GL, the mean actual change for HbA1c from baseline to Month 36 was -1.1% and the mean percent change for triglycerides was -57.6%. Among patients in the PL subgroup, the mean actual change for HbA1c from baseline to Month 36 was -1.6% and the mean percent change for triglycerides was -19.9%.

In comparison with results provided in the Evaluation Consultation Document response as part of the original submission, where 12-month data only was provided in subset of patients, concerns of the ERG have been addressed by providing analysis using both long-term data and for all patients who have been treated with metreleptin at Addenbrooke's Hospital as of January 2020 (87).

Table 23: Results from Early Access Programme at Addenbrooke's Hospital

Study name		Addenbrooke's Hospital Early Access Programme data		
Size of study groups	**Treatment**	GL = 10 PL subgroup[a] = 18 PL overall = 21		
Study duration	**Time unit**	Ongoing		
Change from baseline in HbA1c (%)				
		GL N = 10	PL subgroup[a] N = 18	PL overall N = 21
Baseline value	**n**	9	18	21
	Mean (SD)	9.6 (2.37)	8.3 (2.34)	8.0 (2.30)
Month 12 value[b]	**n**	7	5	6
	Mean (SD)	8.8 (2.41)	7.2 (0.08)	7.2 (0.09)
Month 36 value[c]	**n**	3	4	5
	Mean (SD)	8.9 (3.05)	6.5 (0.62)	6.5 (0.54)
Effect size: actual change from baseline at Month 12[b]	**n**	6	5	6
	Mean (SD)	-1.5 (2.41)	-1.1 (2.04)	-0.8 (1.97)
Effect size: actual change from baseline at Month 36[c]	**n**	3	4	5
	Mean (SD)	-1.1 (6.88)	-1.6 (1.52)	-1.2 (1.61)
Change from baseline in triglycerides (mmol/L)				
		GL N = 10	PL subgroup[a] N = 18	PL overall N = 21
Baseline value	**n**	10	17	20
	Mean (SD)	6.4 (5.06)	4.7 (5.74)	4.2 (5.40)
Month 12 value[b]	**n**	7	5	6
	Mean (SD)	4.6 (4.21)	3.2 (2.18)	3.2 (1.96)
Month 36 value[c]	**n**	3	4	5
	Mean (SD)	4.1 (4.91)	1.8 (1.83)	1.6 (0.69)
Effect size: percent change from baseline at Month 12[b]	**n**	7	4	5
	Mean (SD)	-48.4 (20.30)	-30.8 (32.95)	-22.3 (34.25)
Effect size: percent change	**n**	3	3	4
	Mean (SD)	-57.6 (28.02)	-19.9 (42.02)	-23.9 (35.24)

from baseline at Month 36[c]				

Abbreviations: GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; 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]Defined as the 4th visit (Month 12) to Addenbrooke's Hospital where the 1st visit is at baseline i.e. metreleptin initiation.

[c]Defined as any visit to Addenbrooke's Hospital between Month 30 and Month 42

Source: Combined data on file (85,86)

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

The efficacy analyses in the NIH studies 991265/200110769 and the FHA101 study 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. Similarly, Addenbrooke's Hospital Early Access Programme data included analysis from all patients known to have received at least one dose of metreleptin.

9.7 Adverse events

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 metreleptin trials were identified in the SLR and were described previously (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 *NIH studies 991265/20010769*

Patient exposure

Patient exposure is discussed in Section 9.4. Among patients with GL, 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. (17).

For the PL subgroup, 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 (17).

Adverse events

As concluded by the EMA, the overall safety profile of metreleptin is considered acceptable (81) - a summary of treatment-emergent adverse events (TEAEs) is shown in Table 24. 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. 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%) (17).

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 (reported in 22 (33%) of the 66 GL patients and in 13 (42%) of the 31 patients in the PL subgroup). 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. 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 (17).

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). The types of SAEs were consistent with the underlying lipodystrophy disease, including reports of abdominal pain, pancreatitis, pneumonia, sepsis, and liver disorders. 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 experienced a drug-related SAE (17).

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 TEAEs causing withdrawal led to death (17). None of the deaths were assessed as drug-related.

The majority of the most commonly reported events in the GL group were

consistent with the expected pharmacologic effects of metreleptin, including weight decrease, hypoglycaemia, and decreased appetite, or were gastrointestinal (GI) disorders or constitutional symptoms, including abdominal pain and headache. 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 decrease (15 patients, 23%) and hypoglycaemia (8 patients, 12%) (17).

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 (3 patients with each, 10%) (17).

Table 24: Adverse events: NIH studies 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

	GL (N = 66)	PL subgroup[a] (N = 31)	PL overall (N = 41)
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

Source: NIH studies 991265/20010769 CSR.(17)

9.7.2.2 Study FHA101: supportive evidence

In general, when considering the difference in sample size, the types and incidence of commonly reported TEAEs in study FHA101 were similar to those reported in the pivotal NIH studies 991265/200110769. 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. 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%) (66). Further details of patient exposure of TEAEs is shown in Section 17.10, Table 91.

9.7.2.3 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 lipodystrophy type. Section 17.11, Table 92 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 lipodystrophy studies NIH studies 991265/200110769 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 (17,66).

Selected adverse reactions

Pancreatitis

One of the primary metabolic abnormalities in patients with lipodystrophy is severe hypertriglyceridaemia, which can result in life-threatening bouts of acute pancreatitis. In NIH studies 991265/200110769, where medical history was more consistently recorded than in study FHA101, 31% of patients (33 of 107) reported a history of pancreatitis (17).

Across the 148 patients included in both lipodystrophy studies, 6 (4%) patients (4 with GL and 2 with PL), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and hypertriglyceridaemia so were predisposed to recurrent episodes of recurrent pancreatitis. One of the patients who developed septic shock concurrent with pancreatitis died; the other 5 patients recovered and continued treatment (17,21,66). Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. As noted in the SmPC, 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 (21).

Serious infections

A significant number of patients with acquired forms of lipodystrophy have low C3 levels and the presence of polyclonal immunoglobulin C3 nephritic factor, increasing the risk of recurrent bacterial infections (6).

In NIH studies 991265/200110769, serious infections were reported in 7 (11%) of 66 patients with GL and in 2 (7%) of 31 patients in the PL subgroup. 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 (17). In study FHA101, no serious infections were reported in the GL group or in the PL subgroup (66).

Hypoglycaemia

Metreleptin may decrease insulin resistance in diabetic patients owing to the direct effect metreleptin has on the insulin receptor substrate (IRS)/phosphatidylinositol 3 kinase (PI3K), resulting in hypoglycaemia in patients with lipodystrophy and co-existing diabetes (90). Hypoglycaemia, deemed as related to metreleptin treatment, occurred in 14.2% 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. Generally the majority of events could be managed by food intake with only relatively few modifications of anti-diabetic medicine dosage occurring (21).

T-cell lymphoma

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. 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 (ALCL) was reported in a paediatric patient receiving the medicinal product who did not have haematological abnormalities before treatment. For this patient, metreleptin dosing was held on due to the SAE of ALCL but restarted after biopsy (21).

Immunogenicity

In clinical trials (studies NIH 991265/20010769 and FHA101), the rates of antidrug antibodies (ADAs) in GL and PL patients with data available were 88% (65 out of 74 patients) (21).

A blocking activity of the reaction between metreleptin and a recombinant leptin receptor has been observed *in vitro* in the blood of the majority of an extended set of patients (98 out of 102 patients or 96%) but the impact on the efficacy of metreleptin could not be clearly established. Serious and/or severe infections that were temporally associated with > 80% blocking activity against metreleptin occurred in 5 GL patients. One serious and severe infection (causing appendicitis) was temporally associated with blocking activity against metreleptin in a patient with PL who was not in the subgroup of PL patients. Though temporally associated, it is not possible to unequivocally confirm or deny a direct relation to metreleptin treatment based on the currently available

body of evidence. Lipodystrophy patients with a blocking activity against metreleptin and concurrent infections responded to standard of care treatment (21).

Injection site reactions

Injection site reactions were reported in 3.4% of patients with lipodystrophy treated with metreleptin. All events reported in clinical studies in patients with lipodystrophy 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 (21).

Paediatric population

Across the two completed clinical studies (NIH 991265/20010769 and FHA101), there were 52 paediatric subjects (4 in the PL subgroup and 48 with GL) enrolled and exposed to metreleptin. Limited clinical data exists in children less than 2 years old for GL patients and less than 12 years old in PL patients (21).

Overall, the safety and tolerability of metreleptin are similar in children and adults. In GL patients, the overall incidence of drug-related adverse reactions was similar regardless of age. SAEs were reported in 2 paediatric patients, worsening hypertension and anaplastic large cell lymphoma. In PL patients, assessment across age groups was limited, due to the small sample size. No adverse reactions were reported in paediatric patients in the subgroup of PL patients (21).

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

The EMA has concluded that safety profile of metreleptin is acceptable (81). 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 leptin levels <12 ng/mL and HbA1c ≥6.5% and/or 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 including 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 (17,21,66).

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

9.8 Evidence synthesis and meta-analysis

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.

As described in Section 9.3 and 9.4, there are no head-to-head clinical studies comparing metreleptin with or without supportive care to supportive care alone within this ultra-rare disease. As such, an indirect treatment comparison has been undertaken to generate comparative effectiveness estimates for metreleptin with or without supportive care to supportive care alone using two single-arm studies, with new, updated methods in-line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 17 methods.

Study selection

An SLR and search for unpublished data has been undertaken to identify the relevant studies available for metreleptin with or without supportive care and supportive care alone (Section 9.1 to 9.3). The pivotal metreleptin study is the single-arm NIH 991265-20010769 study. The NIH follow-up study extended the 991265-20010769 study by undertaking a chart review to collect long-term data and additional outcomes for patients with lipodystrophy who received metreleptin therapy at the NIH. The study is based on the patients included in the original study (991265-20010769). This long-term data from the NIH follow-up study was used for the metreleptin data in the indirect treatment comparison where individual patient level data was available (16).

The SLR identified 35 observational studies in patients who are not treated with metreleptin and are receiving supportive care (see Section 9.3). The key relevant study identified, the GL/PL Natural History study (15), was an observational chart review study conducted in one of the same centres (the NIH) as the NIH studies 991265-20010769, in patients who have not received metreleptin treatment (15). As individual patient level data were available for this study and accessed by Amyrt Pharmaceuticals DAC, this supported the use of methods selecting on observables to minimise bias in order to estimate an average treatment effect of metreleptin with or without supportive care to

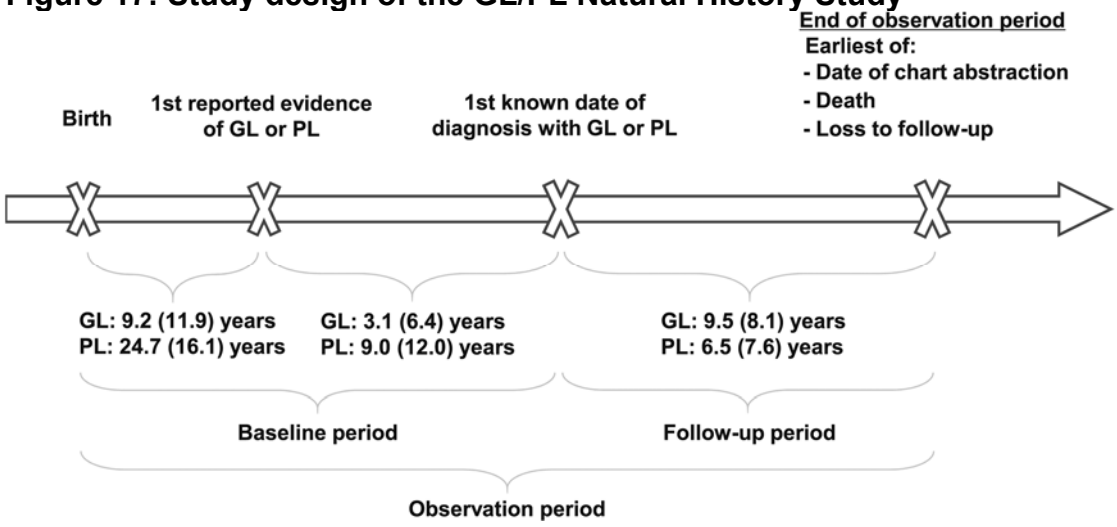
supportive care alone through an indirect comparison treatment comparison. The GL/PL Natural History study is described in more detail below.

GL/PL Natural History study

The GL/PL Natural History study is based on an international chart review of 230 patients with GL or PL (15). To capture data across the entire time period for which data were available within each patient medical chart, the study observation period was defined as the time period that spanned from birth until loss to follow-up, death, or date of chart abstraction, whichever occurred first.

The study design is presented in Figure 17 (15,91). The date when the first signs of lipodystrophy appeared (e.g. visible lipodystrophy, diagnosis of diabetes and/or insulin resistance, and elevated triglycerides or liver enzymes) was denoted as the "first reported evidence of GL or PL." Any time prior to the initial diagnosis of GL or PL was defined as the "baseline period," and any time on or following this diagnosis was defined as the "follow-up period." The date of last available data in each medical chart, at which a patient may be lost to follow-up, deceased, or still alive and being followed at their respective treatment centres, marked the end of the observation period for all patients.

Figure 17: Study design of the GL/PL Natural History Study



Abbreviations: GL, Generalised lipodystrophy; PL, Partial lipodystrophy. Years are given as mean (standard deviation).
Source: Akinci 2019 (15)

Data were collected from 230 leptin therapy-naïve patients (81 patients with GL and 149 patients with PL) receiving supportive care, seen at treatment centres in three countries: US (n=98), Turkey (n=80) and Brazil (n=52). Patient demographic and clinical characteristics are reported by type of lipodystrophy in

Table 25 (15,91).

Patients in the GL/PL Natural History study were generally less severe than patients in the NIH follow-up study. For instance, HbA1c was elevated (≥6.5%) in 74% of GL patients and 71% of PL patients in the NIH follow-up study compared with 43% of GL patients and 53% of PL patients in the GL/PL Natural History study (15,17). Therefore, forming conclusions on the relative efficacy of metreleptin with or without supportive care compared to supportive care alone through a naïve comparison of the NIH follow-up study and the GL/PL Natural History study would be unreliable.

Table 25: Patient Demographic and Clinical Characteristics in the GL/PL Natural History Study

	Overall (N = 230)	GL (n = 81)	PL (n = 149)
Age at first symptoms in y, mean (SD)	19.2 (16.5)	9.2 (11.9)	24.7 (16.1)
Age at initial diagnosis in y, mean (SD)	26.2 (18.4)	12.3 (13.7)	33.7 (16.1)
Age at first visit to treatment centre in y, mean (SD)	28.7 (18.2)	16.1 (13.9)	35.6 (16.6)
Years from first symptoms to diagnosis, mean (SD)	6.9 (10.8)	3.1 (6.4)	9.0 (12.0)
Duration of follow-up period in y, mean (SD)	7.6 (7.9)	9.5 (8.1)	6.5 (7.6)
Males, n (%)	70 (30.4)	33 (40.7)	37 (24.8)
Race/ethnicity,[a] n (%)			
Caucasian/white	166 (72.2)	46 (56.8)	120 (80.5)
African descent/black	17 (7.4)	14 (17.3)	3 (2.0)
Other	21 (9.1)	16 (19.7)	5 (3.4)
Unknown	16 (7.0)	3 (3.7)	13 (8.7)
Country of residence, n (%)			
Brazil	52 (22.6)	25 (30.9)	27 (18.1)
Turkey	80 (34.8)	32 (39.5)	48 (32.2)
United States	93 (40.4)	22 (27.2)	71 (47.7)
Other[b]	5 (2.2)	2 (2.5)	3 (2.0)
Treatment centre, n (%)			
National Institutes of Health (United States)	66 (28.7)	23 (28.4)	43 (28.9)
University of Michigan (United States)	32 (13.9)	1 (1.2)	31 (20.8)
Dokuz Eylül University (Turkey)	80 (34.8)	32 (39.5)	48 (32.2)
Federal University of Ceará (Brazil)	23 (10.0)	19 (23.5)	4 (2.7)
Universidade de São Paulo (Brazil)	29 (12.6)	6 (7.4)	23 (15.4)

Type of lipodystrophy, n (%)			
AGL	7 (3.0)	7 (8.6)	—
APL	28 (12.2)	—	28 (18.8)
CGL	72 (31.3)	72 (88.9)	—
FPLD	121 (52.6)	—	121 (81.2)
Generalised progeroid lipodystrophy	2 (0.9)	2 (2.5)	—

Abbreviations: AGL, Acquired generalised lipodystrophy; APL, Acquired partial lipodystrophy; CGL, Congenital generalised lipodystrophy; FPLD, Familial partial lipodystrophy; GL, Generalised lipodystrophy; PL, Partial lipodystrophy; SD, Standard deviation.
[a]One patient in the United States was marked as "Caucasian" and "Other." Because of this, the sum of patient counts for the race/ethnicity categories may exceed the total number of patients.
[b]Other countries included Argentina, Bahamas, Greece, Israel, and the United Kingdom.

Source: Akinci, 2019, (15)

A variety of outcomes were measured in the GL/PL Natural History study, including organ abnormalities (liver, kidney, heart, pancreas), elevated laboratory values (triglyceride levels, HbA1c, liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and death. No data corresponding to hyperphagia or hunger were collected. (15,91).

9.8.1.1 Indirect treatment comparison

In the absence of head-to-head trials comparing metreleptin with or without supportive care to supportive care alone, an indirect treatment comparison (ITC) has been conducted to estimate the relative difference between key clinical outcomes, focussing on change in HbA1c, triglycerides, ALT and AST from baseline to Month 12; incidence of pancreatitis, and all-cause mortality.

HbA1c, triglycerides, liver enzyme (ALT and AST) levels and mortality were the only outcomes consistently captured and reported in the NIH Follow-up study and the GL/PL Natural History study. As such, these were the only outcomes considered feasible to include as outcomes of interest and were further deemed appropriate through clinician engagement. Although organ abnormality was recorded as an outcome in both studies, there were discrepancies between the definition used in both studies. The only organ abnormality outcome assessed in the ITC analyses was incidence of acute pancreatitis which could be consistently defined across the two studies. Fasting lipids and liver volume were not considered as outcomes of interest because, despite the fact these were recorded in the NIH 991265-20010769 study, the data were not available from the NIH follow-up study. An overall analysis of adverse events as an outcome was not deemed to be feasible to due to differences in safety and tolerability definitions.

The ITC uses two single arm studies, the NIH follow-up study for metreleptin with or without supportive care and the GL/PL Natural History study for supportive care alone. Given the presence of individual patient-level data (IPD) for both studies, methods assuming selection on observables to minimise bias

were used in order to estimate an average treatment effect through an indirect treatment comparison (18).

9.8.1.1.1 Rationale behind adjustment method

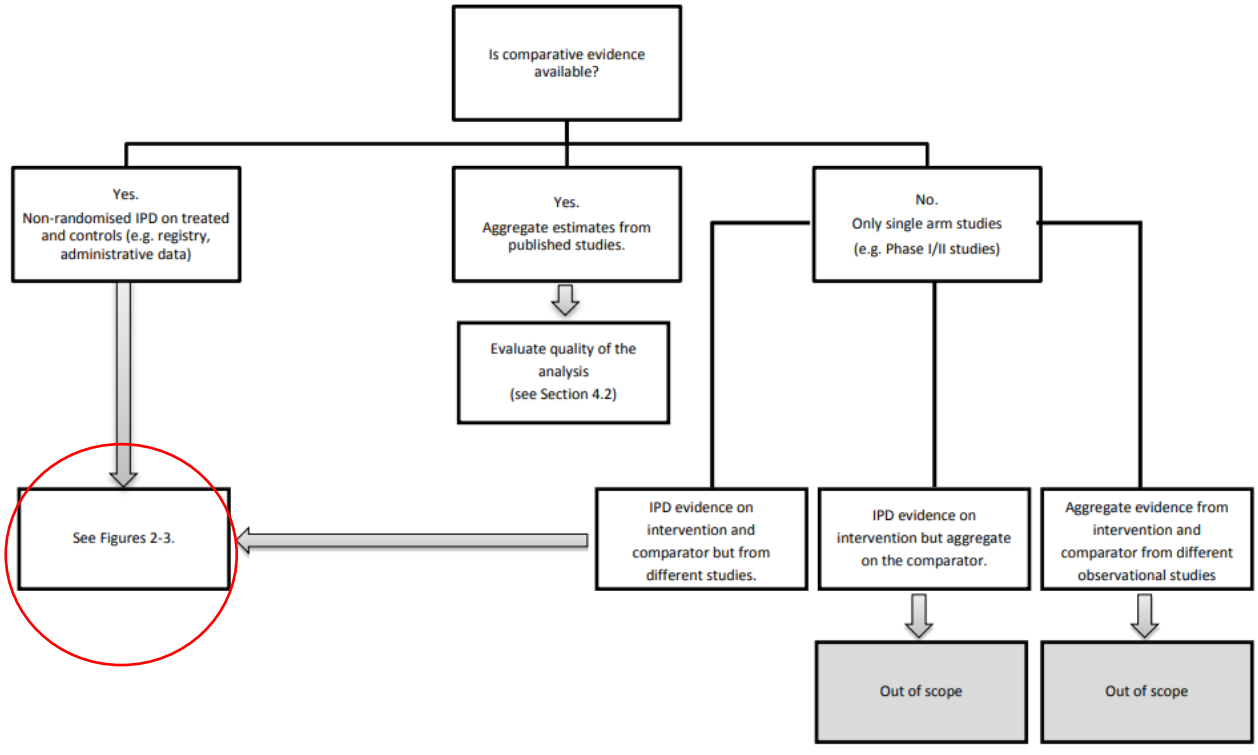
NICE DSU TSD 17 ('The use of observational data to inform estimates of treatment effectiveness in technology appraisal: Methods for comparative individual patient data') (18) was used to inform the statistical methods for the indirect treatment analyses.

Adjustment of the data aims to reduce bias in the estimated treatment effect through the controlling for potential covariates such as age, gender and lipodystrophy type, which may have an independent effect on the outcome of interest or treatment assignment. For instance, patients in the NIH Follow-up study were generally more severe, and thus were younger in age and were more likely to have generalised lipodystrophy. As seen in Figure 18, non-randomised IPD was available for both treated (NIH Follow-up study, metreleptin with or without supportive care) and control (GL/PL Natural History study, supportive care alone) populations, leading to Figure 2 (

Figure 19 in this text) and Figure 3 (

in this text) of the NICE DSU TSD 17.

Figure 18: NICE DSU TSD 17 algorithm used for method selection (Figure 1) (18)



Source: NICE DSU TSD 17 (18)

The non-randomised comparative IPD (supportive care alone) are not from a natural experiment (i.e. there is not a clearly defined exposure and control group within the GL/PL Natural History study). Clinician validation confirmed that the assumption of 'no unobserved confounding' was reasonable – or that patient characteristics that affect the outcomes of interest are observed and accounted for in the methodology. Therefore, a method assuming selection on variables can be followed, leading us to Figure 3 of the NICE DSU TSD 17 (

in this document).

Figure 19: Continued NICE DSU TSD 17 algorithm used for method selection (Figure 2) (18):

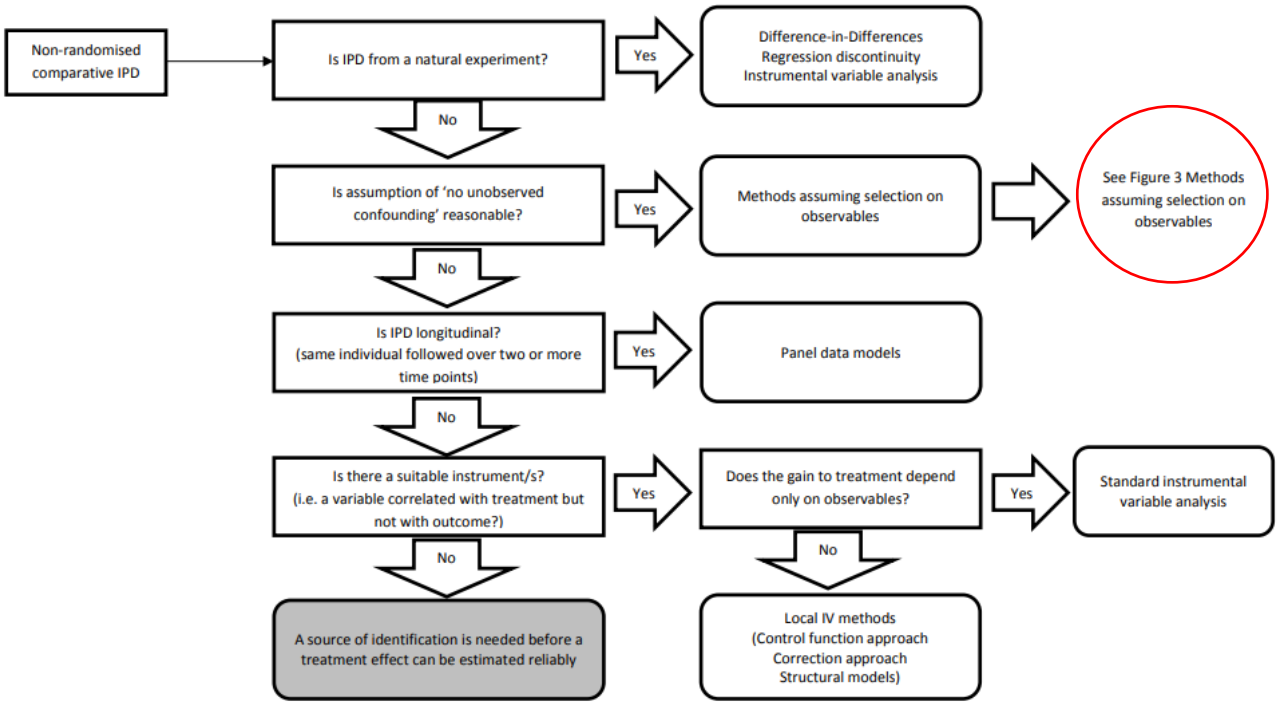
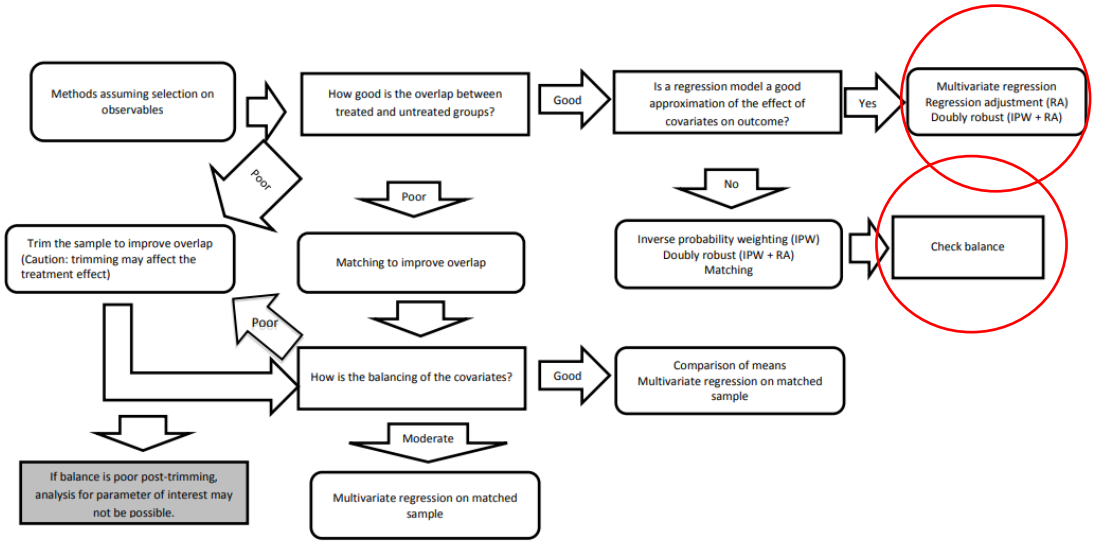


Figure 20: Continued NICE DSU TSD 17 algorithm used for method selection (Figure 3):



Source: NICE DSU TSD 17 (18)

The overlap assumption assumes that for any combination of covariates, there is always the chance of seeing individuals with certain observable characteristics in both the treatment and control groups, ruling out the possibility that some individuals with certain characteristics are always in either the treatment or control group. Therefore, an exploratory histogram comparing the distribution of age in each study was carried out in order to see if there were any areas where the density of covariates was zero for one group, and non-zero for the other (Figure 21). For categorical covariates (i.e. gender and lipodystrophy type), we assessed whether patients were available in all levels of categories in both study types.

Figure 21: Histogram illustrating distribution of age across the GL/PL Natural History study and the NIH Follow-up study

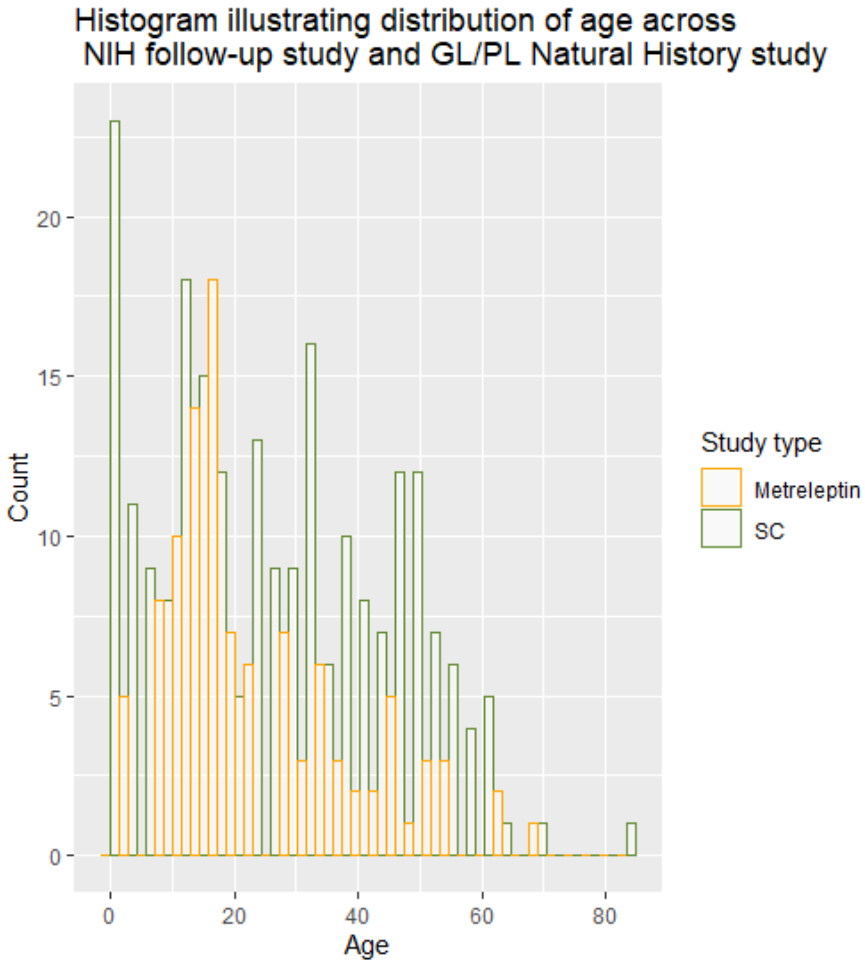


Figure 21 suggests that overlap between age (our only continuous covariate), in the two studies is generally good. As a result of this, two potential appropriate methods were identified: multivariate regression or inverse probability weighting (IPW).

As regression-based methods such as multivariate regression make parametric assumptions about the outcome variable, these assumptions were tested and are reported in Section 17.12.2. These results were presented alongside a sensitivity analysis conducted using a regression-based methodology (multivariate regression), which assessed the normality of fit of the error terms as well as the goodness of fit of the model, confirming that a regression model was not a good approximation of the covariates on the outcome of interest (See Section 17.12.2 and 17.12.4).

Other methodology recommended by NICE TSD DSU 17 include regression adjustment (RA), doubly robust methods such as IPW+RA, and matching (18). As multivariate regression is considered to be a simpler form of RA (18), and a

sensitivity analysis using multivariate regression had been carried out which showed consistent results, it was not deemed necessary to carry out further sensitivity analyses using RA. It has also been suggested that doubly robust methods such as IPW + RA be used as a complement to, as opposed to a substitute for, other methods. (92) As two different approaches exploring regression-based methodology and IPW were utilised, a sensitivity analysis using IPW + RA was not further explored. However, doubly robust methodology may be suitable as a complement to the following analyses.

A further adjustment option which could have been used is matching. However, matching works best if there are a large number of individuals to use in the matching cohort, a large number of covariates to model the propensity score and when the treated and control groups come from the same environment. (18). As our data sets were relatively small, it was not deemed feasible to use methodology in this instance.

9.8.1.1.2 Methodology

Missingness and imputation

Multiple imputation is considered for use when missingness in both arms of a trial (in our case the GL/PL Natural History study and the NIH Follow-up study) is between 5% and 40%, as suggested by Jakobsen *et al.* (2017) (74). In the GL/PL Natural History study, the missingness of data often violated these boundaries. However, in the pancreatitis outcome, missingness in both studies was above 5% and below 40% (shown in bold, Table 26). Thus, only missing pancreatitis values in the GL/PL Natural History study were imputed using the using the **mice** package in R, estimating missing data based on our chosen covariates (age, gender and lipodystrophy type).

Where survival status was unknown at the outcome timepoint, individuals in both studies were censored and presumed to be alive at their last visit date. Therefore, the data set for the mortality outcome could be considered ‘complete’. Furthermore, one additional patient who died early for which no laboratory values were available for was added to mortality analyses, in line with the clinical study report (CSR) (55).

Table 26: Missingness and appropriateness for imputation in NIH Follow-up study and GL/PL Natural History study

Study type	HbA1c	Triglyc-erides	ALT	AST	Pancreatitis	Mortality
Metreleptin w / wo SC (NIH Follow up study)	101/105 (96.19%)	101/105 (96.19%)	99/105 (94.2%)	99/105 (94.2%)	**105/105 (100%)**	106/106* (100%)
Supportive care (GL/PL Natural History Study)	21/228 (9.21%)	46/228 (20.17%)	42/228 (18.42%)	38/228 (16.89%)	**193/228 (84.64%)**	228/228 (100%)

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GL, Generalised lipodystrophy; PL, Partial lipodystrophy; SC, Supportive care; w / wo, with or without.

**106 as one patient who died shortly after metreleptin initiation was included in the analysis*

Baseline and outcome definition

In the NIH Follow-up study, baseline measurements of HbA1c and triglycerides were taken at metreleptin initiation. Baseline measures of ALT and AST were defined as ±3 months from the date of diagnosis, as liver enzyme measures were not explicitly taken at the date of diagnosis. Outcome measures were taken at 1 year ±6 months post metreleptin initiation. Both baseline and outcome measures were required to calculate the change in values, which were used as our outcome.

In the GL/PL Natural History study**,** baseline was defined as ± 3 months from the date of diagnosis. Outcome was defined as 1 year ± 6 months after the date of diagnosis. Several time point definitions were considered for the outcome measure due to the level of missing data, as both the baseline and outcome measure are required to calculate the change. Ultimately, a 1 year ± 6-month time point was chosen in order to maximise the number of individuals with data available whilst remaining as consistent as possible to NIH Follow-up outcome time point.

Our pancreatitis outcome was defined as incidence of pancreatitis throughout the time course of both studies. Similarly, our mortality outcome was defined as instances of death throughout the time-course of both studies.

Statistical methodology

The IPW uses the propensity score (PS) function, which is a function of a set of observed covariates. Each patient's weighting is equal to the inverse of the probability of receiving metreleptin, given the patient's certain characteristics. As IPW uses the inverse of the probability of treatment assignment to weight outcomes, the average treatment effect (ATE) corresponds to the difference in these weighted means. Due to the relatively small sample size in the HbA1c outcome of the supportive care alone arm compared to the metreleptin with or without supportive care arm, stabilized inverse probability weights were used in order to avoid excessively high weights in the supportive care arm (94) .

An ATE was calculated using linear models for continuous outcomes (change in HbA1c, triglycerides, ALT and AST from baseline to Month 12), generalised linear models for categorical outcomes (incidence of pancreatitis) and cox proportional hazard models for time to event outcomes (all-cause mortality), using the propensity score weights as a link function. For continuous outcomes, the ATE was estimated by the mean difference between the two groups using the coefficient of treatment assignment. For categorical outcomes, the ATE was estimated by the odds ratio (OR) using the exponential of the coefficient of treatment assignment. For time to event outcomes, the ATE was estimated by the hazard ratio (HR) using the exponential of the coefficient of treatment assignment.

Robust standard errors were calculated using a robust sandwich estimator to take into account that the IPW uses weighted data.

A naÏve analysis (direct comparing the results in the two groups without any adjustments) was also conducted, the results of which are given in Section 17.12.3.

All statistical analyses were performed using R version 3.6.1.

Covariate and subgroup sensitivity analyses

Potential sensitivity analyses were considered, including the addition of extra covariates (history of baseline elevated HbA1c and elevated triglycerides, baseline leptin levels and baseline pancreatitis) and subgroups (GL and PL who had failed supportive care). These sensitivity analyses were not deemed feasible due to the extent of the missing data in the GL/PL Natural History study, alongside the limited number of mortality and pancreatitis events across the studies.

9.8.1.1.3 Selection of desired covariates

Appropriate variables for the propensity score (PS) regression model are those that enable the model to satisfy the 'ignorability of treatment assumption', to avoid bias (95). Only variables that affect both treatment assignment and the

outcome of interest were included in the model (95). Clinical expert opinion was used to evaluate which covariates met the second part of this condition (change over one-year in HbA1c, triglycerides, ALT and AST; incidence of acute pancreatitis and mortality since treatment initiation). T tests and Chi-squared tests were also conducted to test effect on treatment. The covariates that were included in treatment models the PS model include:

- Gender
- Age at baseline
- Lipodystrophy type

A variety of additional covariates were considered for inclusion in the PS model but were not deemed feasible. For instance, inclusion of baseline leptin, HbA1c elevation, triglyceride elevation, incidence of pancreatitis and liver enzyme levels were not deemed feasible due to the extent of missing data in the GL/PL Natural History study. A full list of baseline characteristics in both studies covariates considered as potential covariates are given in Section 17.12.1.

9.8.1.1.4 Covariate balance

In randomised controlled trials (RCTs), randomisation ensures that the factors affecting outcomes are evenly balanced between treatment groups. This allows us to attribute the outcome to the treatment administered. The purpose of our indirect treatment comparison is to emulate the ATE observed in clinical trials. Thus, it is important to assess the balance of covariates after our adjustment analyses. This is presented through a summary of patient characteristics before and after weighting alongside other checks of covariate balance, including standardized mean differences, variance ratios, Kolmogorov-Statistics and histograms in Section 17.12.5.

9.8.1.1.5 Results

In this section a summary of the ATE of metreleptin with or without supportive care compared to supportive care alone will be given for change from baseline to Month 12 in HbA1c, triglycerides, ALT and AST; incidence of acute pancreatitis and all-cause mortality.

Naïve analyses

The results of our naïve analyses are given in Section 17.12.3.

Adjusted analyses

Mean actual percentage change in HbA1c

Stabilised inverse probability weighting results showed that metreleptin with or without supportive care significantly reduced actual HbA1c by 1.52% compared to supportive care alone at Month 12 from baseline ($p<0.001$) (Table 27).

Table 27: Stabilised inverse probability weighting results showing ATE of metreleptin with or without supportive care compared to supportive care alone in HbA1c change from baseline to Month 12

	Coefficient (mean actual HbA1c, %)	**Robust standard error (%)**	**95% CI (%)**	**p-value**
ATE of metreleptin w / wo SC versus SC	-1.52	0.38	-2.28; -0.77	**<0.001***
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; SC, Supportive care; w / wo, With or without *denotes significance at the p<0.05 level				

Mean mg/dL change in triglycerides

Inverse probability weighting showed that metreleptin with or without supportive care significantly reduced triglyceride levels by 915 mg/dL compared to supportive care alone at Month 12 from baseline (p<0.001). Results converted from mg/dL to mmol/L are shown in square brackets by dividing by 88.5 (Table 28).

Table 28: Inverse probability weighting results showing ATE of metreleptin with or without supportive care compared to supportive care alone in triglyceride change from baseline to Month 12

	Coefficient (triglycerides, mg/dL) [mmol/L]	**Robust standard error, mg/dL [mmol/L]**	**95% CI, mg/dL [mmol/L]**	**p-value**
ATE of metreleptin w / wo SC versus SC	-915.30 [10.34]	225.95 [2.55]	-1358.15; -472.44 [-15.35; 5.34]	**<0.001***
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; SC, Supportive care; w / wo, With or without *denotes significance at the P<0.05 level				

Mean U/L change in ALT

Inverse probability weighting showed that metreleptin with or without supportive care significantly reduced ALT levels by 44 U/L compared to supportive care alone at Month 12 from baseline (p<0.001; Table 29).

Table 29: Inverse probability weighting results showing ATE of metreleptin with or without supportive care compared to supportive care alone in ALT change from baseline to Month 12

	Coefficient (ALT, U/L)	**Standard error**	**95% CI**	**p-value**
ATE of metreleptin w / wo SC versus SC	-44.13	11.06	-65.81; -22.46	**<0.001***
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; SC, Supportive care; w / wo, With or without *denotes significance at the P<0.05 level				

Mean U/L change in AST

Inverse probability weighting showed that metreleptin with or without supportive care significantly reduced AST levels by 28 U/L compared to supportive care alone at Month 12 from baseline (p<0.001; Table 30).

Table 30: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in AST change from baseline to Month 12

	Coefficient (AST, U/L)	**Robust standard error (U/L)**	**95% CI (U/L)**	**p-value**
ATE of metreleptin w / wo SC versus SC	-27.79	6.93	-41.38; -14.20	**<0.001***
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; SC, Supportive care; w / wo, With or without *denotes significance at the P<0.05 level				

Incidence of pancreatitis

Inverse probability weighting showed that metreleptin with or without supportive care significantly reduced the odds of a pancreatitis episode by 6% (odds ratio (OR): 0.94 p=0.0095;

Table 31).

Table 31: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in incidence of pancreatitis

	Coefficient (AST, U/L)	OR	Robust standard error	95% CI of OR	p-value
ATE of metreleptin w / wo SC versus SC	-0.067	0.94	0.026	0.89; 0.98	**0.01***

Abbreviations: OR, odds ratio; ATE, Average treatment effect; CI, Confidence interval; SC, Supportive care; w / wo, With or without

*denotes significance at the P<0.05 level

Incidence of pancreatitis (with imputation)

Inverse probability weighting showed that metreleptin with or without supportive care significantly reduced the odds of a pancreatitis episode by 7% when missing values were imputed (odds ratio (OR): 0.93, p=0.003;

Table 31).

Table 32: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in incidence of pancreatitis (imputed)

	Coefficient	OR	Robust standard error	95% CI of OR	p-value
ATE of metreleptin w / wo SC versus SC	-0.074	0.93	0.026	-0.88; 0.98	**0.004***

Abbreviations: OR, odds ratio; ATE, Average treatment effect; CI, Confidence interval; SC, Supportive care; w / wo, With or without *denotes significance at the P<0.05 level

All-cause mortality

The hazard ratio (HR) of all-cause mortality for metreleptin with or without supportive care vs supportive care alone was estimated to be 1.38, however this was not significant (p=0.42).

Table 33).

Table 33: Inverse probability weighting results showing adjusted ATE of metreleptin with or without supportive care compared to supportive care alone in all-cause mortality

	Coefficient	HR	Robust standard error of HR	95% CI of HR	P-value
ATE of metreleptin w / wo SC versus SC	0.32	1.38	0.40	1.88; 20.37	0.42
Abbreviations: HR, hazard ratio; ATE, Average treatment effect; CI, Confidence interval; SC, Supportive care; w / wo, With or without					

9.8.1.2 Discussion

Comparative effectiveness estimates have been generated using individual patient-level data from two single arm studies comprising the two largest data sets for patients with lipodystrophy. Appropriate methods assuming selection on observables to minimise bias have been used in order to estimate an average treatment effect through an indirect comparison. This has shown a statistically significant benefit in key efficacy endpoints as a result of metreleptin, including a 1.52% reduction in HbA1c and a 915 mg/dL (10.34 mmol/L) reduction in triglyceride levels.

Within the GL/PL Natural History study and the NIH Follow-up study, there were imbalances in key prognostic variables for which adjustment was required: patients in the NIH Follow-up study were generally more severe, and were thus likely to be younger with a greater incidence of generalised lipodystrophy. IPW is recommended as an option by NICE DSU (TSD 17) when IPD from both treatment arms is available, the assumption of 'no unobserved confounding' is reasonable, and regression is not considered to be a good approximation of the covariates on the outcome of interest. We confirmed the suitability of a regression based methodology through the parametric assumption (Section

17.12.2) as well as a sensitivity analysis assessing the goodness of fit and normality of the error terms of our models (Section 17.12.4).

This ITC estimated an ATE for individuals receiving metreleptin with or without supportive care compared to supportive care alone using IPW. The covariates that were included in the propensity score model included gender, age at baseline and lipodystrophy type. Individuals receiving metreleptin with or without supportive care had a significantly greater change in HbA1c, triglycerides and liver enzymes over the course of a year, compared to individuals receiving supportive care alone. In line with recommendations with the NICE TSD DSU 17, we explored the impact of using alternative regression-based methods, namely multivariate regression (Section 17.12.4). The results are generally comparable across the alternative methodologies, indicating robustness in our results.

Though all possible steps were taken to assess the feasibility of gaining robust results from IPW analyses, a limitation of any method to account for patient heterogeneity across treatment arms is that it is not possible to account for all unobserved confounding variables. These are variables which either could not be or were not measured in the either the GL/PL Natural History study or the NIH follow-up study. Hence, the results are potentially inherently biased to the nature of any such methodology which aims to infer treatment effect by adjusting for covariates.

Secondly, we encountered typical challenges when assessing ultra-rare populations, such as small sample sizes and missing data in the observational GL/PL Natural History study. The small sample size in which complete data for both baseline characteristics and outcomes were available may have impacted some of our results. For example, as a relatively small amount of patients in the supportive care arm were present with both baseline and outcome measures in HbA1c, excessively large weights were allocated, which vastly reduced the statistical power, although the results did show a statistically significant result. However, it is important to note that there was a relatively low amount of missing data for the pancreatitis outcome. Furthermore, our results were very similar when imputing missing data in this instance, adding to their reliability.

Neither the NIH follow-up study nor the GL/PL Natural History study were powered to evaluate significant differences in mortality. Mortality analyses were limited by the number of events observed, with both follow-up time period in the NIH Follow-up study and small sample size in both studies contributing to this low number. Though we had a complete data set, only 32 events were observed across both the GL/PL Natural History study and the NIH Follow-up study, which had a variety of implications. Firstly, if we follow the ‘one in ten rule’ – that every covariate added to a model should have at least ten events

supporting its presence, we are at risk of overfitting our model (as we have three covariates in addition to our exploratory covariate of interest, treatment group). However, it has been argued that this rule is too conservative, and should be relaxed (96,97). Regardless, we cannot rule out the possibility that our coefficient (and thus our hazard ratios) and p-values are inflated, making our results less reliable.

In conclusion, ITC analyses using a NICE DSU-informed methodology (IPW) generated robust statistically adjusted estimates of the treatment effect of metreleptin with or without supportive care relative to supportive care alone for change in HbA1c, triglycerides, ALT at Month 12 from baseline, and incidence of pancreatitis. These analyses confirmed the clinical efficacy of metreleptin, previously demonstrated through NIH studies 991265/200110769 and supported through data from the EAP.

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.

Not applicable.

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 clinical data (studies NIH 991265/20010769) supporting the EMA Marketing Authorisation of metreleptin and the indirect treatment comparison demonstrated that metreleptin in both GL and PL patients significantly improved the management of blood sugar and triglyceride (blood lipid) levels which can be severely raised in lipodystrophy patients and are difficult to manage (27).

Clinically meaningful improvements in HbA1c consistent with improvement in insulin sensitivity:

In NIH studies 991265/200110769, 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 (17). Furthermore, the indirect treatment comparison demonstrated a -1.52% change in HbA1c in metreleptin compared to supportive care from baseline to Month 12 representing a clinically meaningful change in HbA1c (Section 9.8.1.1; Table 27) and is consistent with a pooled GL/PL

population. The naïve comparison of the mean HbA1c change of metreleptin compared to supportive care at Month 12 compared to baseline prior to the weighting adjustments showed an absolute difference of -1.66 (95% confidence interval: -0.90 to -2.35) for the pooled lipodystrophy population (see Table 93). Following the stabilised IPW adjustment used in the ITC, the mean change was -1.52 (95% confidence interval: -0.77 to -2.28). As such, this also demonstrated observed reductions NIH studies 991265/200110769 (17) are representative of comparative data for metreleptin in comparison with supportive care.

Clinically meaningful improvements in triglycerides:

In NIH studies 991265/200110769, mean relative 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 (17).

Not all patients in the study 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 (17).

In NIH studies 991265/200110769, among 45 patients with GL who had a baseline HbA1c of ≥8% available at Month 12, the mean (SD) baseline HbA1c was 9.9% (1.48) and the mean reduction in HbA1c at Month 12 was -3.0%. Among 24 patients with GL who had a baseline triglyceride level ≥5.65 mmol/L 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 PL subgroup who had a baseline triglyceride level ≥5.65 mmol/L 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% (17). In addition, the indirect treatment comparison demonstrated an estimated a 915 mg/dL (10.34 mmol/L) reduction in triglycerides in metreleptin compared to supportive care from baseline to Month 12 representing a clinically meaningful change in triglyceride (Section 9.8.1.1; Table 28)

Clinically meaningful reductions in HbA1c and triglycerides were sustained over long-term treatment:

Most patients received 2 or more years of therapy with a maximum duration of 14 years; total patient-years of exposure across the lipodystrophy studies exceeded 500 years. Long term results of the primary endpoint in studies NIH 991265/20010769 up to 48 months in GL and 36 months in the PL subgroup showed sustained clinically meaningful improvements in HbA1c and triglyceride levels. Furthermore, based on the results of the mixed models repeated measures (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 studies NIH 991265/20010769 (17). Complementary evidence from Addenbrooke's Hospital Early Access Programme provides support for this, with sustained improvements in glycaemic control and hypertriglyceridaemia in both GL and PL subgroup patients observed up to 36 months (Section 9.6).

Target responses of ≥1% in HbA1c and/or ≥30% in triglycerides were observed:

In NIH studies 991265/200110769, 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 (17).

Clinically meaningful improvements in pancreatitis:

From the NIH follow-up study, results indicated post-metreleptin improvement in pancreatitis occurred in 95% (20 of 21) of GL patients and in 100% (23 of 23) PL patients where data available (16). The indirect treatment comparison suggested a 6-7% reduction in the odds of an episode of pancreatitis on metreleptin compared to supportive care, corresponding to an OR of 0.94-0.93. (Section 9.8.1.1,

Table 31; Table 32).

Clinically meaningful improvements were observed in elevated hepatic enzymes and hepatomegaly, commonly used surrogate measures of hepatic steatosis:

In NIH studies 991265/200110769, 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 (17).

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 by Javor *et al*. 2005, Petersen

et al. 2002 and Safar-Zadeh *et al.* 2013 (32,65,98), and are supported by an indirect treatment comparison suggesting a 44 U/L (Table 29) and 28 U/L (Table 30) reduction in ALT and AST, respectively (Section 9.8.1.1).

Long-term follow-up data of metreleptin treatment in lipodystrophy patients over several years indicate an overall favourable tolerability profile:

Adverse events are generally consistent with that of a patient population with significant co-morbidities. The identified risks including 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 (17,21,66).

Long-term follow-up data of metreleptin treatment in lipodystrophy patients over several years indicate treatment with metreleptin leads to a significant improvement of the metabolic state:

In some of the patients with GL who received co-medications at the baseline, treatment with insulin, oral antidiabetics or lipid lowering therapies could be discontinued. Among the 39 patients with GL who were receiving insulin at baseline, 16 (41%) were able to discontinue insulin use altogether after starting metreleptin. Most of these patients (13 of 16) were able to stop insulin use within the first year of metreleptin. For the 32 patients with GL who were receiving oral anti-diabetic medicinal products at baseline, 7 (22%) were able to discontinue their use. A total of 8 (24%) of the 34 patients with GL who were receiving lipid-lowering therapies at baseline discontinued their use during metreleptin treatment (81). Complementary evidence from a Delphi panel conducted by Amyrt showed that 5% (CI: 0-10%) of patients with PL treated with metreleptin can completely discontinue insulin treatment; 50% (95% CI: 40-60%) of patients with PL treated with metreleptin can completely discontinue oral antidiabetic medication other than metformin; 51% (95% CI: 26-75%) of patients with PL treated with metreleptin can completely discontinue triglyceride-lowering medication.

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%]).

10 Measurement and valuation of health effects

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

Lipodystrophy is characterised by complete or partial loss or absence of subcutaneous adipose tissue (2, 88) resulting in reduced fat storage capacity and leptin deficiency (see Section 6.1.1 for further details). As a result of this patients suffer from a complex range of conditions, including but not limited to ectopic fat accumulation in organs, insulin resistance, diabetes and hypertriglyceridaemia. Patients with lipodystrophy are, as a result, prone to developing various metabolic disorders and serious complications leading to high morbidity, significantly impaired quality of life and premature mortality (2,100).

Lipodystrophy is associated with several metabolic abnormalities associated with insulin resistance including diabetes, hypertriglyceridaemia, and a variety of liver abnormalities such as hepatic steatosis. In itself, poor metabolic control is associated with a lower quality of life. A study by Ali *et al.* (2018) suggested that impaired blood sugar and impaired triglyceride control are associated with utility decrements of -0.079 and -0.112, respectively (101). For context, renal complication associated with dialysis and transplant are associated with utility decrements of −0.082 and −0.053, respectively (102). In addition, as a result of these metabolic complications, patients may develop several chronic complications which have a substantial effect on quality of life such as pancreatitis, renal failure, and cardiovascular disease. Often these organ complications drastically decrease quality of life by increasing overall pain, requiring further medication and leading to premature death: liver, kidney, heart and pancreatitis damage have been associated with utility decrements of -0.153, -0.128, -0.187 and -0.128 respectively, demonstrating the substantial impact of organ damage on quality of life (101). Furthermore, hyperphagia, a state of hunger likened to starvation is also detrimental to quality of life with an estimated utility decrement of -0.11 (68), and often arises as a result of poor metabolic control in lipodystrophy driven by leptin deficiency.

Amongst the many consequences of lipodystrophy, psychological disturbances such as anxiety, depression and fatigue are often particularly understated but have a substantial effect on quality of life. Patients may have difficulty attending school or work or carrying out day to day tasks, which has a substantial effect on QoL (associated with a utility decrement of -0.255 (87)). Depressive

symptoms are often compounded due to the impaired physical appearance associated with lipodystrophy, leading to low self-esteem.

An overview of lipodystrophy-related complications, clinical consequences and impact on patient quality of life has previously been outlined in Table 8.

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.

Lipodystrophy is a progressive, chronic disease, resulting in a complex range of complications developing over multiple organs, ultimately resulting in premature mortality (2,100). Age of diagnosis of the first organ abnormality estimated to be 12.9 years (15). As such, as metabolic disease and organ damage worsen over disease progression, it results in a progressive decline in HRQoL over time. The rapid progression of organ damage ultimately has a significant impact on QoL, with the associated utility decrement in the lead up to a year before metreleptin administration estimated to be -0.162 over time (101).

GL patients are characterised by a general lack of adipose tissue at birth or shortly after. This is accompanied by a variety of symptoms as a consequence of a lack of adipose tissue, including hypertriglyceridaemia, hyperphagia as a result of underlying leptin deficiency, acromegaloid features and hyperinsulinemia at a young age (5). This results in a vastly reduced quality of life from early childhood, which is likely to continue into adulthood, especially if patients do not receive a clear-cut diagnosis.

PL patients may have a relatively normal body fat distribution until around puberty, associated metabolic abnormalities arise in early adulthood and ultimately result in many of the lipodystrophy-associated complications such as a variable lack of adipose tissue leading to hypertriglyceridaemia, pancreatitis and cardiomyopathies. (5)

Furthermore, acquired forms of lipodystrophy tend to present with a progressive lack of fat tissue in childhood or adolescence over a period of months to years, though sometimes as rapidly as a few weeks (5), resulting in a progressive deterioration in HRQoL. In addition, acquired forms of lipodystrophy are associated with later development of autoimmune disease (103) such as rheumatoid arthritis (104) and Crohn's disease (105).

HRQL data derived from clinical trials

10.1.3 If HRQL 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 pivotal clinical trials led by NIH 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 pivotal clinical trials led by NIH, no mapping was undertaken.

HRQL studies

10.1.5 Please provide a systematic search of HRQL 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.

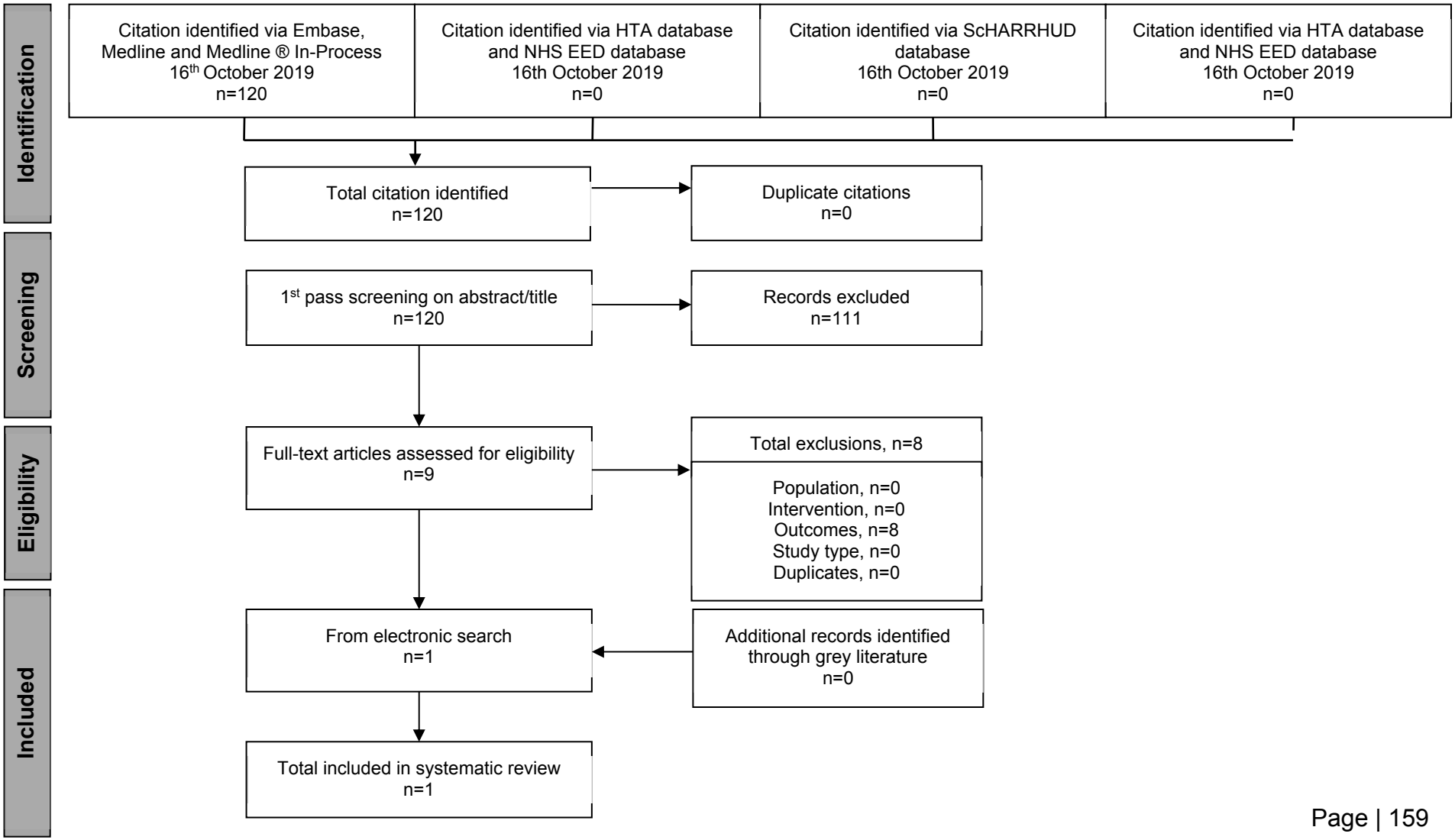
Details of the SLR to capture HRQL data are provided in Appendix 5, Section 17.5. The inclusion and exclusion criteria used in the SLR are outlined in Table 67.

Figure 22 below displays the schematic for the updated economic, cost and resource use and HRQL SLRs. This schematic displays references which were found from January 2017 to 16th October 2019, since the original searches were run.

The previous SLRs conducted, which were accepted by the ERG, originally found 2 HRQL references for data extraction. PRISMA diagrams for the

previous HRQL SLR can be found in Appendix 5, section 17.5.2 (Figure 38). This figure displays references which were found from 2006 (inclusive) to January 2017.

Figure 22: Schematic for the economic, cost and resource use, and HRQL SLR



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.**

One publication reporting HRQL was identified in the SLR. Ali *et al.* conducted a discrete choice experiment (DCE) with 1,000 members of the general population, in order to characterise the health utility consequences of GL and PL patients, as well as assess the QALY gains associated with leptin replacement therapy (metreleptin).

Multinomial logit regression was used to estimate utility decrements associated with different quality of life (QoL) attributes including impaired work/school ability, hyperphagia and organ damage. Results were combined with data on prevalence of attributes before and after one year of leptin replacement therapy to assess overall QoL consequences, and the impact of leptin replacement therapy on QALYs (101).

The study indicated that lipodystrophy is associated with large QoL impairment and that the benefits of leptin replacement therapy may be substantial. QALY gains associated with leptin replacement therapy were estimated at 0.423 across all patients (Table 34) . A subgroup analysis found that GL patients had total QALY gains of 0.569 and PL patients of 0.199.

Table 34: Summary of HRQL study details

Reference	Population	Elicitation Method	Valuation Method	Total QALY gain
Ali *et al.* 2018 *Abstract*	n=114 61% GL, 39% PL	DCE	N=1,000 General Population	Overall:0.423 GL:0.569 PL:0.199
Abbreviations: DCE – Discrete choice experiment; GL – generalised lipodystrophy; PL – Partial lipodystrophy; QALY – Quality-adjusted life year				

Source: Source: Ali, 2018 (101)

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 possible, 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 HRQL.

The adverse event data is described in more detail in Section 9.7**Error! Reference source not found.**. The most common drug-related treatment emergent adverse events (TEAEs) in the NIH 991265/20010769 and FHA101 studies were mild to moderate in severity, such as abdominal pain, decreased appetite or headache. Most severe TEAEs were consistent with known symptoms or complications of lipodystrophy (e.g. renal failure, cardiac arrest and pancreatitis), and were not considered to be drug related.

One key drug-related complication identified was hypoglycaemia. As metreleptin lowers the effect of insulin resistance in patients with lipodystrophy with diabetes, there is an increasing risk of hypoglycaemia as doses are titrated. However, this was assumed to have a minimal impact on HRQoL given the short duration of symptoms.

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.

As described in section, 12.1.3, the cost-effectiveness model includes several health states encompassing a wide range of co-morbidities affecting multiple organs, including cardiovascular, liver, kidneys and pancreas. There are over 30 health states included in the model across six sub-models representing different organ-related complications. In such situations, the Decision Support Unit TSD 12 (106) recommends obtaining health state utility values from cohorts with combined health conditions. As such, where available, utility values were drawn from the UKPDS 62 sub-study by Clarke *et al.* (107). where patients with type 2 diabetes were followed up for 30 years and experienced multiple complications across multiple organs covering a number of diabetes-related health states included in the *de novo* cost-effectiveness model. Lipodystrophy leads to insulin-resistant diabetes (see section 6.1), and therefore is a common characteristic in lipodystrophy patients. Therefore, it has been assumed these data are generalisable to the specific population of interest in the *de novo* cost-effectiveness model.

In the UKPDS 62, the EQ-5D instrument was administered to 3,667 UKPDS patients with type 2 diabetes to estimate the impact of diabetes-related complications on utility-based measures of quality of life. Patients were followed up for 30 years in UKPDS and has been widely used as a source of utility values and accepted in multiple NICE appraisals in type 2 diabetes, e.g. TA288, TA336 and TA390 (108–110). In obtaining these values, a likelihood ratio test was performed to determine whether a significant difference existed between the coefficients for the disutility if the event occurred within the previous year or more than one year ago. When significant differences were not found between these coefficients for the disutility, a single utility decrement was generated based on the assumption that the effect of compilations on utility does not vary over time. For all health states within the model drawn from the UKPDS 62 sub-study, the difference between these coefficients were found to not be significant. Therefore, the same disutility values were applied in the event year and post event-year for relevant health states drawn from the UKPDS 62 sub-study.

Utility values for the liver sub-model were informed using the NICE NAFLD guidelines (25). Utility decrements for each health state were calculated by deducting the utility values for each of the health states from the utility value for the ‘NAFL-NASH (F012) – treated’ health state. The utility decrements for

compensated cirrhosis with varices and decompensated cirrhosis with varices health states were assumed to be the same as the utility decrements for the compensated cirrhosis and decompensated cirrhosis health states respectively.

The utility value for acute pancreatitis was drawn from the previous metreleptin submission (111), as a suitable alternative value was not available in the literature. The value was obtained by means of a discrete choice experiment (DCE) within the general population. Respondents in the US (250) UK (150), France (150), Germany (150), Italy (150), and Spain (150) were surveyed (1,000 respondents in total). 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. Choice cards represent hypothetical patients and were constructed by assigning values to disease attributes of interest and varying these values across the 2 cards. After collecting these data, standard QALY estimation techniques derived from academic literature were applied to generate QALY decrements associated with the relevant disease attributes, as described in the previous metreleptin submission (111).

As outlined in Section 6.1.1 lipodystrophy is associated with a number of complications, which significantly impact patient QoL. Some of these complications such as hyperphagia, dysmorphia PCOS and female reproductive dysfunction have not been captured within the organ-specific sub-models. In order to account for such complications, a disutility of 0.13, drawn from the previous metreleptin submission for hyperphagia alone (111) was applied to patients treated by SC alone. This was generated by means of a DCE, as outlined for the pancreatitis utility decrement above. Despite the limitations with DCEs, an alternative value could not be sourced from literature.

A caregiver burden decrement was also applied. This was calculated by evaluating the difference between the general population norm, taken from the EQ-5D UK-specific TTO value for the equivalent age group (112,113), and the average EQ-5D TTO value for caregivers, taken from the *Lipodystrophy Caregiver Burden Survey* (see section 7) (12). The average age of caregivers from the *Lipodystrophy Caregiver Burden Survey* was 43.7.

The utility decrements were applied to age-dependent utility baseline values for UK population norms (112,113), as further described in section 10.1.14.

Any remaining data gaps were filled from other published sources and those previously used and accepted in relevant NICE appraisals, as specified in the table below.

Table 35: Summary of quality-of-life values for cost-effectiveness analysis

Parameter	Base-case value	Source	Justification
Liver sub-model utility decrements			
Asymptomatic liver disease	-0.03	NAFL-NASH (F012) utility from NAFLD NICE guideline (25)	Consistency with NAFLD NICE guideline
Advanced fibrosis	-0.15	Fibrosis F3 utility from NAFLD NICE guideline (25)	
Compensated cirrhosis	-0.27	NAFLD NICE guideline (25)	
Decompensated cirrhosis	-0.33		
Compensated cirrhosis with varices	-0.27		
Decompensated cirrhosis with varices	-0.33		
Variceal bleeding	-0.33		
Hepatocellular carcinoma	-0.33		
Liver transplant	-0.07		
Post liver transplant	-0.02		
CVD sub-model utility decrements			
Angina	-0.09	NICE TA288, TA366, TA390 (108–110); Clarke *et al.* (UKPDS) (107,108)	EQ5D, UK sample and value set
Stroke	-0.164		
Congestive heart failure	-0.108		
Myocardial infarction	-0.055		
Kidney sub-model utility decrements			
Microalbuminuria	0	NICE NG17 (114)	Conservative estimate, consistent with NICE NG17
Macroalbuminuria	-0.048	Beaudet *et al.* (115)	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case. The disutility applied was assumed to equal the disutility for proteinuria (consistent with costing approach for macroalbuminuria).
End stage renal disease	-0.222	NICE TA358; Lee *et al.* (116)	EQ-5D, UK sample and value set
Kidney transplant (year 1)	-0.148	NICE TA358; Clinical opinion (117)	Consistency with NICE TA358 submission, from which the utility value for the post-kidney transplant (year 2+) value was sourced.
Post kidney transplant (year 2+)	-0.082	NICE TA358; Lee *et al.* (116,117)	EQ-5D, UK sample and value set
Pancreatitis sub-model utility decrements			
Acute pancreatitis	-0.13	NICE ID861 (111)	Suitable value not available from literature
Retinopathy sub-model utility decrements			
Background retinopathy	-0.027	NICE TA597; Peasgood *et al.* (118,119)	EQ5D, UK sample and value set

Proliferative retinopathy	-0.07	NICE TA597; Beaudet *et al.* (115,119)	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case
Macular oedema	-0.04	NICE TA597; Beaudet *et al.* (115,119)	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case
Blindness	-0.074	NICE TA597; Clarke *et al.* (UKPDS)(107,119)	EQ5D, UK sample and value set
Neuropathy sub-model utility decrements			
Peripheral neuropathy	-0.084	NICE TA597; Beaudet *et al.* (115,119)	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case
Amputation	-0.28	NICE TA288, TA366, TA390 (108–110); Clarke *et al.* (UKPDS) (107,108)	EQ5D, UK sample and value set
'Other symptoms' decrement			
'Other symptoms'	-0.22	Assumption	Significant impact on QoL not captured in sub-models
Caregiver burden decrement			
Caregiver burden	-0.0986	Janssen *et al.*; Kind *et al.* Caregiver Burden Survey (7,112, 113)	Inclusion of caregiver disutility has been accepted in previous NICE HST submissions for similarly devastating diseases (120)
Age-specific general population values			
<18	0.94	Assumption	HRQoL declines with increasing age
18 – 24	0.94	Janssen *et al.* (112); Kind et al. (113)	
25 – 34	0.927		
35 – 44	0.911		
45 – 54	0.847		
55 – 64	0.799		
65 – 74	0.779		
75+	0.726		

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

- **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**

[2] 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.

- **whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).**

Clinical experts were not used to supply or verify values for parameters used in the economic model. However, a number of discussions were held with a health economic expert during which the model and input parameters were discussed in order to strengthen the model and analyses.

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

If a patient experiences a lipodystrophy-related complication, a decrement is applied to the specific age-dependent baseline utility. The model assumes that for patients experiencing complications in more than one organ, the decrements associated with each organ are applied to the baseline value using a multiplicative approach, as recommended in NICE TSD12 (106). As such, the relevant decrements are combined proportionally (relative to baseline) to generate a single decrement applied to the age-adjusted baseline utility values, accounting for multiple events occurring across the separate sub-models.

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 for metreleptin identified and summarised in section 9.4.

There is published and unpublished data that has been identified and shared previously with NICE with respect to utilities in lipodystrophy patients. Due to the new model structure, the main utility values have been sourced aligned to the health states and standard UK population norms based on EQ-5D and using TTO to align with NICE's reference case.

There is one published source of utility data that has been excluded from the analysis. Firstly a conference abstract published by Dhankhar *et al.* (51) in 2015, which is reported and described in section 7.1. The average EQ-5D score for lipodystrophy patients was not considered useful because estimates were based on a group of respondents which included patients without lipodystrophy. Therefore, there may be some bias in the results if some of the respondents are carers of patients with lipodystrophy or if participants who incorrectly think they have lipodystrophy have completed the HRQoL questionnaire. Furthermore, applying organ-specific disutility values to this estimate would result in double-counting and a subsequent underestimation of utility.

10.1.13 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

As described in section 10.1.6, age-adjusted baseline utilities have been used and thus baseline utility values decrease over time with age. Furthermore, patients' HRQoL decline over time due to the chronic and progressive nature of lipodystrophy, with patients experiencing complications across multiple organs. In the model, HRQoL declines as the disease advances through the organ-specific health states, and the health state-specific decrements are applied multiplicatively. Besides the liver sub-model, organ progression cannot be reversed for any organ. Once a patient is diagnosed with an organ-specific complication, organ health can only progress further, or the patient can die.

10.1.14 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?

It was assumed that age-dependent utility values for the UK population are representative of a lipodystrophy patient without any symptoms, who would be expected to have a relatively unaffected QoL. Therefore, an age-dependent utility value corresponding with age at baseline was assumed as baseline quality of life in the analyses. Quality of life events were taken from this baseline. Age-dependent EQ-5D utility values were derived from an inverse relationship between age and utility that were obtained using a representative sample from the UK population (112).

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

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.**

The cost-effectiveness model incorporates a stopping rule to reflect those patients that will benefit the most from metreleptin based on measures routinely assessed in UK clinical practice.

In the SmPC for Myalepta, a minimum clinical response is defined as at least:

- 0.5% HbA1c reduction and/or 25% reduction in insulin requirements

  and/or

- 15% reduction in triglycerides (TGs).

If a clinical response is not seen after 6 months of treatment the physician should ensure that the patient is compliant with the administration technique, is receiving the correct dose and is adherent to diet. Consider dose increase before stopping treatment.

Working in collaboration with clinicians at Addenbrooke's Hospital we have agreed the following stopping criteria based on their clinical experience with the EAP and the proportion of new patients anticipated to stop treatment.

Guidance for stopping metreleptin treatment in PL: At 9 months after metreleptin initiation, a Specialist Service review will determine whether treatment should be stopped for PL patients if the following metabolic criteria have not been met: a HbA1c reduction of at least 0.75% from baseline, or a fasting triglyceride reduction of at least 50% from baseline.

The Specialist Service may agree to continue metreleptin therapy in occasional patients with PL who have not met the above metabolic criteria but who are judged by the Specialist Service to have had other significant treatment benefits such as a very significant reduction in concomitant medication, significant improvement in NAFLD, and/or a significant improvement in quality of life due

to for example a significant appetite reduction, or in whom a trial of dose escalation is thought to be required.

Due to higher HbA1c and triglyceride reductions observed in the GL group compared with the PL group in the pivotal NIH studies 991265/200110769 (see section 9.4). such a metabolic stopping rule would likely be successfully achieved by the majority (if not all) GL patients. Given the near universal development of fatty liver disease in patients with GL and the consistent reduction in liver fat seen with metreleptin treatment, a strong case can be made for life-long treatment of patients with GL, even if the HbA1c and triglyceride criteria for continuation are not met.

As HbA1c and triglycerides are routinely measured at Addenbrooke's Hospital standard disease management appointments, the implementation of this metabolic stopping criteria for new PL patients fits within current monitoring practice.

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

Identification of studies

11.1 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.

Details of the SLR strategy to capture health economic data and studies relevant to the decision problem are provided in Section 17.3 (Appendix 3).

11.1.1 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.

The inclusion and exclusion criteria used in the SLR are outlined in Section 17.3 (Appendix 3).

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

No economic publications were identified from the updated SLR. Figure 22 (Appendix 5) displays the schematic for the updated economic evidence, resource identification and HRQL SLRs. The PRISMA diagram for the previous submission can be found in Appendix 3 (Figure 37). The previous SLR retrieved a total of 3 studies, 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 submission owing to the population studied.

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 patient population considered in the cost-effectiveness model analyses is aligned to the licensed indication for metreleptin (21) and is:

• Adults and children above the age of 2 years with generalised lipodystrophy (GL).

• Adults and children above the age of 12 years with partial lipodystrophy (PL), when standard treatments have failed to achieve adequate metabolic control.

The baseline characteristics representative of patients with GL and PL are summarised in Table 36. These were based on the NIH studies 991265/200110769.There is a lack of published data concerning the prevalence and incidence of GL and PL relevant to the licensed metreleptin population. However, given the availability of directly relevant and representative EAP data from a decade of metreleptin use in UK clinical practice, these figures were used to determine the proportion of patients with GL or PL for use in the CEM.

Table 36: Baseline characteristics, patients with GL and PL

Type of lipodystrophy	Proportion of patients (%)	Female (%)	Mean age (years)
GL	43.48%	77.3	Male: 19.5 Female: 17.3 Overall: 17.8
PL	56.52%	96.8	37.0
Abbreviations: GL, Generalised lipodystrophy; PL, Partial lipodystrophy			

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

The comparator for the analysis is supportive care (SC), which is representative of the use of medications currently used to manage metabolic complications, such as lipid-lowering and anti-hyperglycaemia therapies. This is consistent with the scope. Diet lifestyle modifications are a mainstay of disease management irrespective of treatment, and therefore is considered distinct from supportive care.

The introduction of metreleptin in England is expected to displace or reduce supportive care in lipodystrophy patients.

See Section 8 for further details regarding the current management of patients.

Model structure

12.1.3 Provide a diagram of the model structure you have chosen.

To evaluate the cost-effectiveness of metreleptin, a *de novo* individual patient-level model has been constructed addressing the prior concerns raised by the NICE Committee (1). The metabolic model has been developed in collaboration with clinical experts at Addenbrooke's Hospital and via a Delphi Panel consisting of 10 UK & international clinicians (23) to reflect disease progression and clinical management of the disease.

The model structure is shown in Figure 23. The model consists of six Markov sub-models simulating the progression of disease on key, distinct organ systems, capturing key lipodystrophy-related complications which have major impacts on health-related quality of life, costs and mortality during the lipodystrophy disease lifetime. These models simulate the progression of multiple organ systems affected by as described in Section 6.1.2 and 6.1.3). In each simulation, a patient is simultaneously in a discrete health state in each of

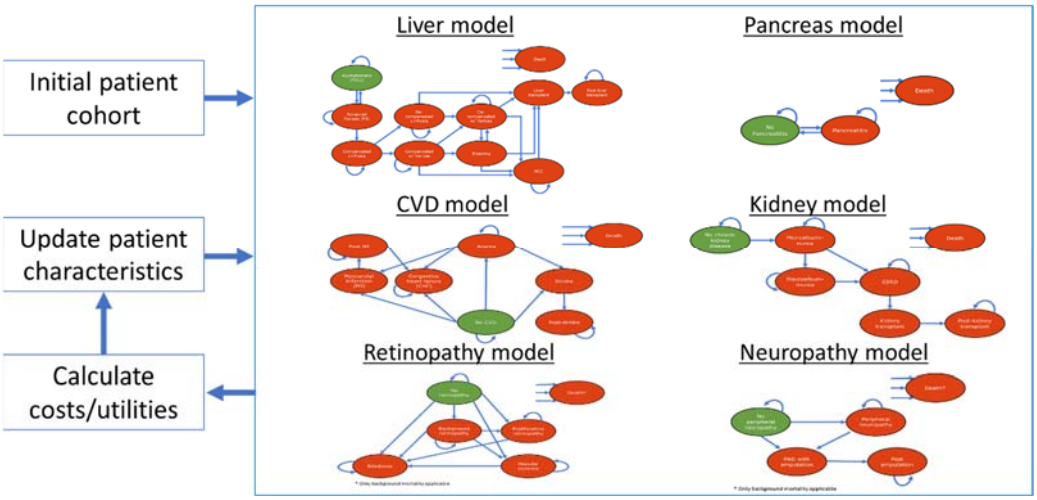
the six independent sub-models. The six sub-models are independent and that the patient is simultaneously in a discrete health state in each of the six models during each cycle. A patient may die during each cycle, in which case the patient will be removed from all models into a death state.

Sub models

The model comprises of the following six Markov sub-models:

- Pancreas
- Liver disease
- Cardiovascular disease
- Kidney model
- Neuropathy
- Retinopathy

Figure 23: Individual patient-level model structure



Abbreviations: CVD, Cardiovascular disease

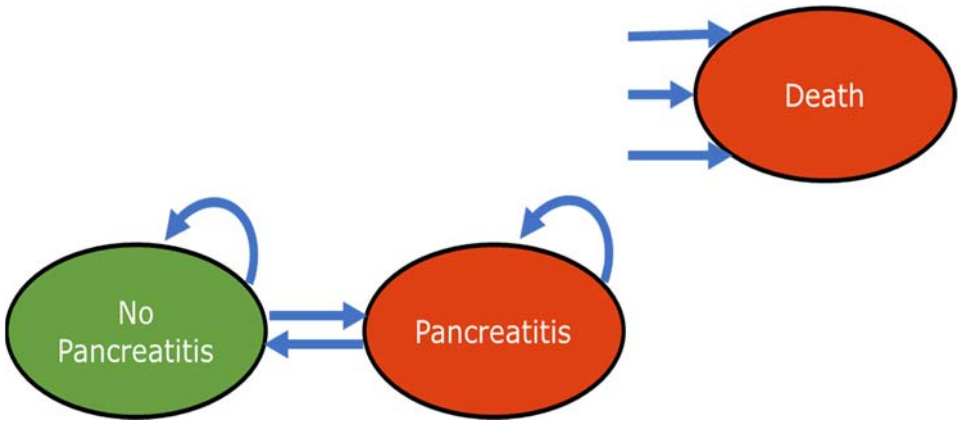
A more detailed analysis of the model structure in terms of individual health states and transitions is available in section 12.1.4.

Pancreas sub-model

As described in section 6.1.3.1.1 and supported by UK clinical experts and the Delphi panel (23), GL and PL patients are at are at higher risk of pancreatitis, especially those with raised triglyceride levels. As such, the inclusion and

structure of this model are based on the widespread onset of acute pancreatitis in lipodystrophy patient studies as well as the availability of high-quality pancreatitis data for lipodystrophy patients (2,26). **Error! Reference source not found.**Figure 24 outlines the model structure for the pancreas sub-model. Only, three states are present; absence of pancreatitis, pancreatitis and death related to the onset of pancreatitis.

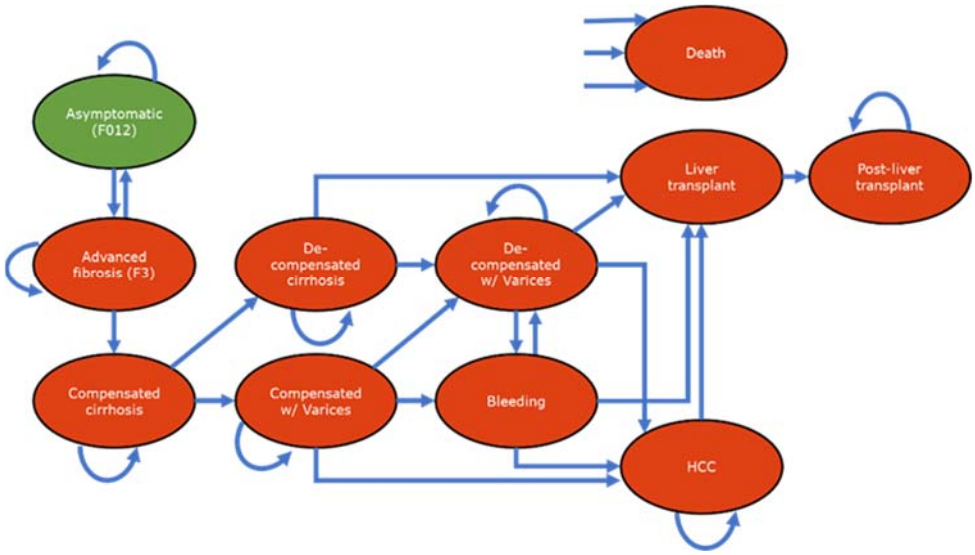
Figure 24: Pancreatitis sub-model structure



Liver sub-model

As described in section 6.1.3.2 and supported by UK clinical experts and the Delphi panel (23), lipodystrophy patients are at risk of non-alcoholic fatty liver disease (NAFLD) (specifically NASH). as a result of ectopic fat deposition, leading to the development of complications such as cirrhosis and hepatic cell carcinoma. As such, the liver sub-model structure aims to model liver disease complications as mediated by lipodystrophy using the pathogenesis of NAFLD/NASH as an analogue for lipodystrophy patients suffering from with liver disease. The model structure has been based on the *de novo* cost-effectiveness model developed for the NICE NAFLD guideline (NG49) and is summarised in Figure 25 below (25).

Figure 25: Liver sub-model structure



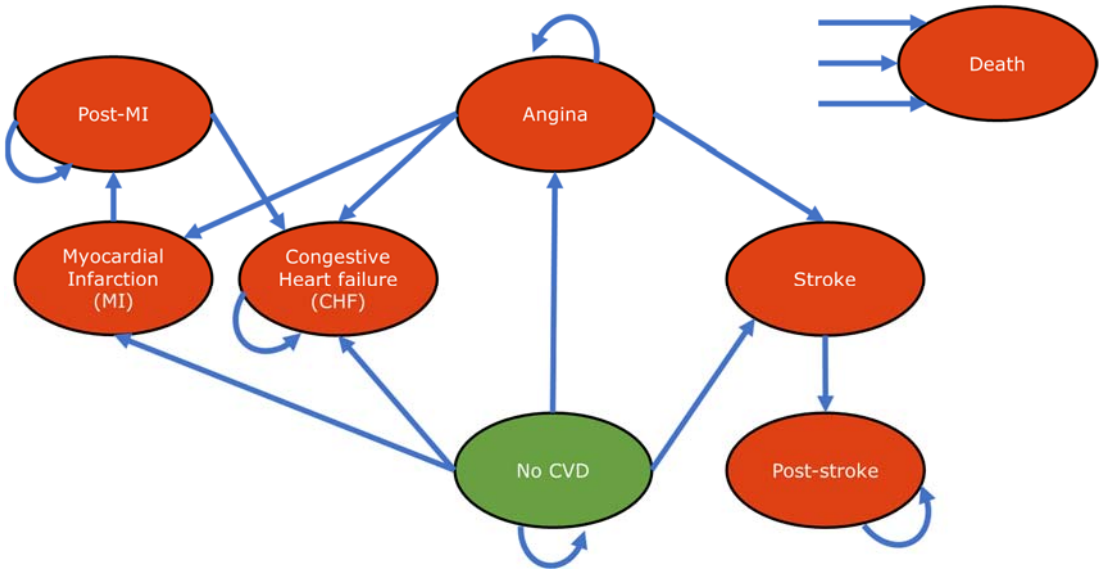
Abbreviations: F, Fibrosis; HCC, Hepatic cell carcinoma

Patients transition through health states, from having asymptomatic fibrosis, advancing through advanced fibrosis to compensated and de-compensated cirrhosis. Advanced fibrosis is reversible, and thus patients are able to transition from advanced fibrosis to asymptomatic disease. Compensated and decompensated cirrhosis can worsen to become compensated or decompensated cirrhosis with varices (respectively), and from those states patients may transition to bleeding (one-off event) and HCC (hepatocellular carcinoma). Patients can also undergo liver transplant from decompensated cirrhosis, bleeding or HCC. The transplant state in liver disease model represents the acute surgical phase, while the post-transplant state models patients' long-term health after transplantation. Besides the transplant state, states in the liver model are all continuous, meaning patients can remain within any of the health states. Patients can die from any health state, with elevated mortality risks associated with the decompensated cirrhosis, bleeding and HCC health states.

Cardiovascular sub-model

As described in section **Error! Reference source not found.** and validated by UK clinical experts and the Delphi panel (23), GL and PL patients are at higher risk of cardiovascular disease, especially those with hypertriglycerideamia and diabetes (i.e. elevated HbA1c). As such, the cardiovascular Markov sub-model structure simulates these cardiovascular complications due to lipodystrophy. The model health states included have been based on a review of a previously accepted NICE models for cardiovascular disease and the literature to reflect the common complications observed in lipodystrophy patients (24,121,122). The model structure is outlined in Figure 26.

Figure 26: Cardiovascular sub-model structure



Abbreviations: CHF, Congestive heart failure; CVD, Cardiovascular; MI, Myocardial infarction

The cardiovascular Markov model structure aims to simulate the incidence of four cardiovascular complications (angina, congestive heart failure [CHF], myocardial infarction [MI] and stroke); these were the most prominent in previous cardiovascular models and most commonly experienced by lipodystrophy patients (2). Although patients are at risk of cardiomyopathy, these was not included due to a lack of transition probability data identified in the literature.

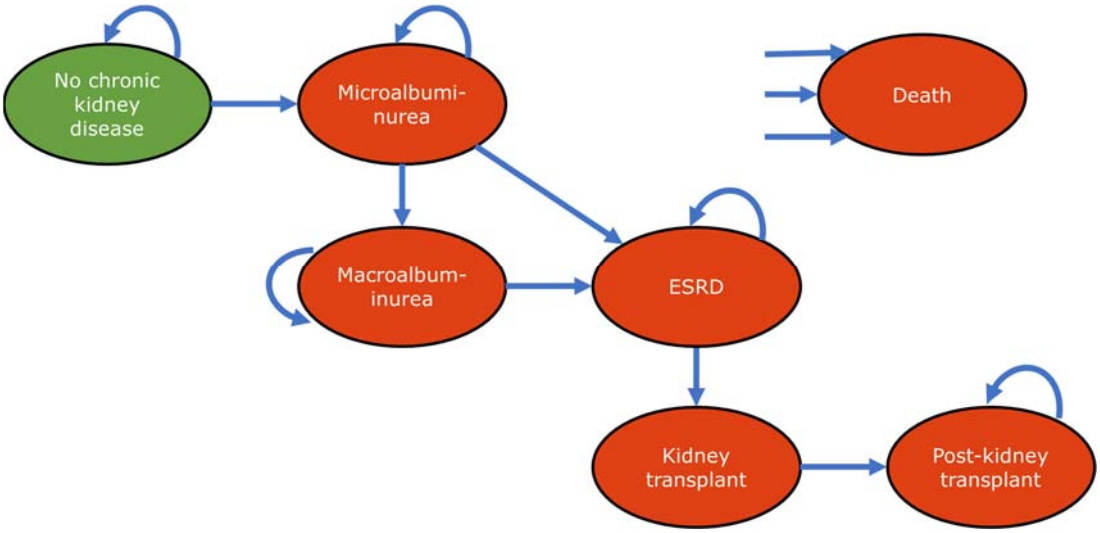
Patients begin with no cardiovascular disease and are at risk of experiencing cardiovascular complications in each cycle. MI or stroke health states are tunnel health states representing the acute stage (including rehabilitation) of the condition, with patients subsequently state moving to post-MI or post-stroke health states representing the long-term maintenance of the condition. Patients may enter acute event states (stroke and MI) only once but can subsequently remain in continuous event states (Post-MI, Post-stroke and CHF). Patients can die from cardiovascular reasons from any health state except No CVD (and from background mortality regardless of state), with patients at an elevated risk of mortality from more severe health states (see Section 12.2.1 for further details).

Kidney sub-model

As described in section 6.1.3.4 and validated by UK clinical experts and the Delphi panel (23), GL or PL patients are at are at higher risk of kidney disease, especially those with diabetes (i.e. elevated HbA1c).

The structure of the kidney sub-model reflects the common kidney complications associated with lipodystrophy. This is consistent with the structure from the Sheffield diabetes model (24), and has been validated with UK clinical experts. The model structure is shown in Figure 27.

Figure 27: Kidney sub-model structure



Abbreviations: ESRD, End stage renal disease

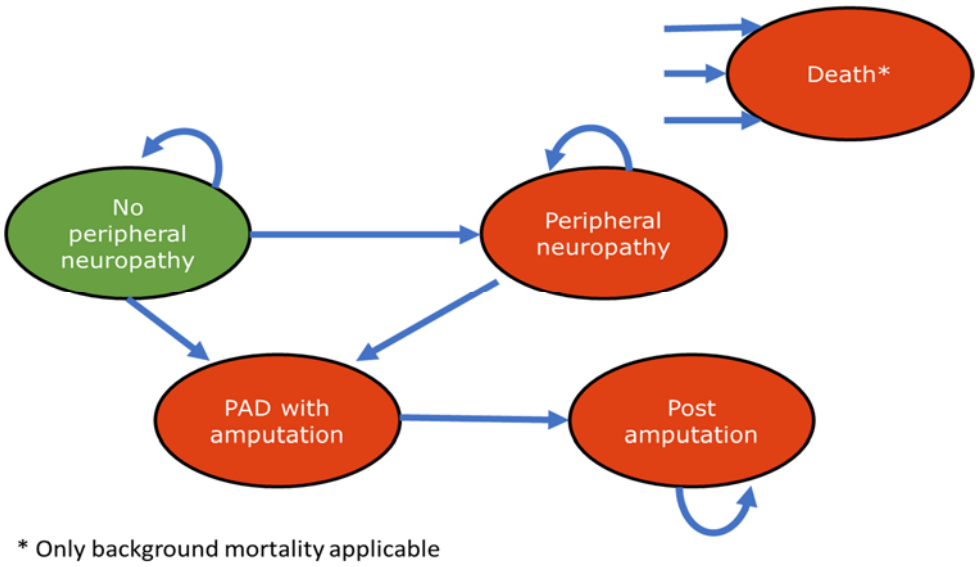
Patients can transition through health states representing the severity of kidney disease, with patients starting with no chronic kidney disease, moving through microalbuminuria and macroalbuminuria to the end stage renal disease (ESRD) health state. From ESRD patients can transition to require a kidney transplant, moving to post-transplant state in the following cycle. The kidney transplant health state represents the acute surgical phase, while the post-transplant state considers the long-term health state after transplantation. Patients can die from kidney related complications from any health state, and from background mortality from any state (see Section 12.2.1 for further details).

Neuropathy sub-model

As described in section 6.1.3 and validated by UK clinical experts and the Delphi panel (23), patients with generalised or partial lipodystrophy are at are at higher risk of neuropathic disease, especially those with diabetes (i.e. elevated HbA1c).

The neuropathic disease sub-model structure reflects the neuropathic and peripheral vascular specific elements of microvascular complications associated with lipodystrophy. Figure 28 outlines the model structure for neuropathic complications.

Figure 28: Neuropathy sub-model structure



Abbreviations: PAD, peripheral arterial disease

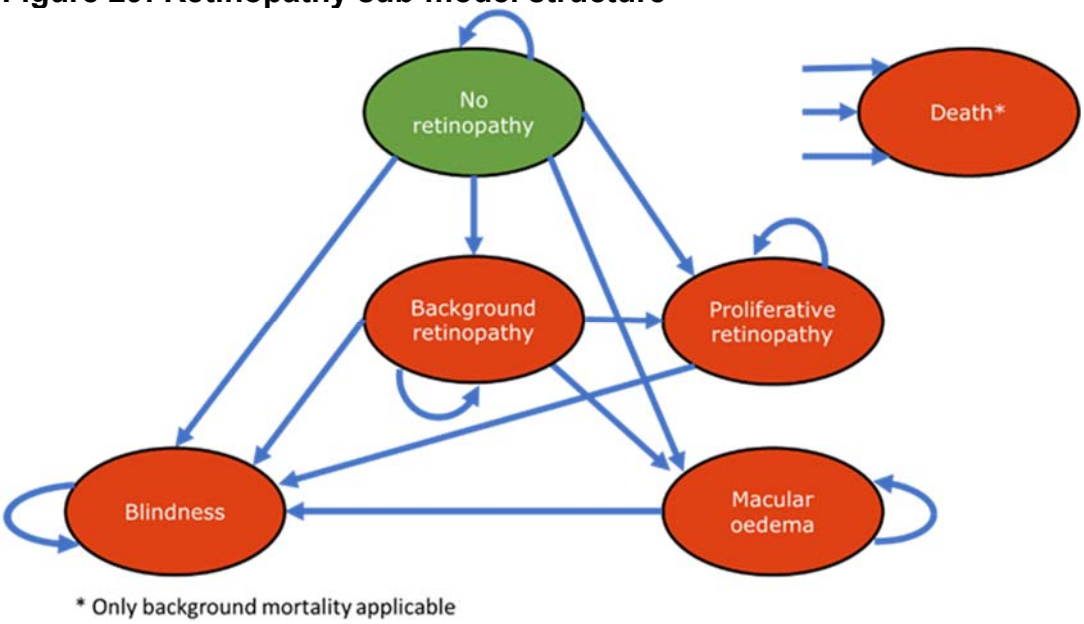
There are four health states: no peripheral neuropathy, peripheral neuropathy, peripheral arterial disease (PAD) with amputation and death. Patients can remain in any of the alive health states in each cycle. Patients can die from any health state based on background mortality rates (see Section 12.2.1 for further details). Death is included as it has an impact on costs and utilities.

Retinopathy sub-model

As described in section 6.1.3 and validated by UK clinical experts and the Delphi panel (23), GL and PL patients are at are at higher risk of retinopathy, especially those with diabetes (i.e. elevated HbA1c).

The retinopathy disease model structure simulates retinopathy-specific microvascular complications associated with lipodystrophy. Figure 29 shows the retinopathy model structure.

Figure 29: Retinopathy sub-model structure



Patients begin the model with no retinopathy complications, and can progress to blindness either directly, or by progressing through various retinal diseases such as background retinopathy, proliferative retinopathy and macular oedema. Patients can remain within any of the alive health states in each cycle. Patients can die from any health state based on background mortality rates (see Section 12.2.1 for further details). Death is included as it has an impact on costs and utilities.

Patient characteristics

Baseline characteristics have been sourced from the NIH studies 991265/20010769 (as described in section 9.4), as UK clinical experts and NICE have agreed that these patients are generalisable to UK clinical practice (1). As described in section 6, lipodystrophy is heterogeneous group of disorders, with disease progression and diagnosis varying between GL and PL patients. As such, to reflect the differences, baseline characteristics aligned to each population are used in the model and these are probabilistically employed in the base case using the gamma distribution based on the standard deviations.

Attributes of patients in each treatment arm either remain constant or evolve according to specified rules that reflect disease progression. As outlined in section 12.1.1, the proportion of patients with GL or PL have been derived from EAP data from a decade of metreleptin use in UK clinical practice. Attributes of patients in each treatment arm either remain constant or evolve according to

specified rules that reflect disease progression. Table 37 outlines the baseline inputs used in the model.

Table 37: Baseline characteristic inputs from the NIH studies 991265/20010769 (27,80)

Baseline parameters	GL	PL
Female (%)	77.3	96.8
Mean age (years) [SD]	Male: 19.5 [18.10] Female: 17.3 [17.3]	37.0 [14.37]
HbA1c (%) [SD]	Male: 8.1 [2.52] Female: 8.8 [2.25]	8.8 [1.88]
Weight (kg)	Male: 55.1 [20.22] Female: 51.9 [18.58]	68.7 [14.67]
Abbreviations: GL; Generalised lipodystrophy, PL; Partial lipodystrophy, HbA1c; Heamoglobin A1C; SD, Standard deviation		

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

Lipodystrophy is a progressive, chronic condition, which interacts with several organ systems during the patients' lifetime. The impact of lipodystrophy can include premature mortality driven by the development and subsequent worsening of organ conditions. Additionally, lipodystrophy impacts patient's quality of life via hyperphagia, pain, and depression, female reproductive dysfunction, and the dysfunctions from organ damage. These conditions have the potential for interaction with a cumulative effect on patient quality of life, and they are present from an early age, in GL particularly. The probability of experiencing each of these outcomes will depend on baseline characteristics, previous events, and response to therapy.

Previously published cost-effectiveness models were evaluated to inform the structure for the *de novo* model. Three cost-effectiveness studies were identified in HIV-related populations; while these populations are not included in the licensed indication for metreleptin, they provide useful analogues to help inform the model design. Two studies were from a United States perspective and one from a Canadian perspective. Model structures varied across these studies, which included a decision tree and Markov, a Markov and a discrete simulation model.

Two previous model structures were submitted for this appraisal. Firstly, an individual patient-level model approach was submitted. The structure aimed to model lipodystrophy disease lifetime through organ abnormalities, categorised as the heart, liver, kidneys and pancreas. Due to concerns around the model

structure and inputs from the NICE committee, a second model was submitted. This consisted of a partitioned survival analysis modelling approach, which focused purely on the mortality element of lipodystrophy. In the previous two CEMs submitted to NICE as part of the appraisal for metreleptin, there were several concerns raised by NICE as reflected in the FED for metreleptin (1). It stated concerns that disease progression of lipodystrophy over time was not reflected in the model. The clinical experts explained that there was a lack of real-world data outlining the progression of lipodystrophy in people who have not had metreleptin. The committee acknowledged that evidence was sparse but agreed it would have preferred a model that attempted to capture the disease progression over time. Additionally, the committee further noted that metabolic, surrogate outcomes (such as HbA1c and triglyceride level) could be used to extrapolate outcomes in the model, and a diabetes or fatty liver model basis would be more appropriate would be more appropriate to use as the basis for the model.

The model structure presented in section 12.1.3 seeks to align with the committee recommendations by creating a *de novo* model informed by an existing diabetes model and NAFLD model to model the disease progression of lipodystrophy and the associated complications. The model is based on the structure on the diabetes-related complications observed in the Sheffield diabetes model (24), as well as the model structure from the NICE NAFLD guideline to reflect liver disease progression The model adopts the use of hard outcomes from the NIH and GL/PL Natural History study , through an indirect treatment comparison (ITC), as well as surrogate outcomes which are clinically advised to be suitable indicators of disease progression by the Delphi Panel (23), derived from individual patient data. Inputs from data elicited from clinical key opinion leaders in lipodystrophy through the Delphi panel were also used as data inputs for the model (23).

While actual organ complication comparisons between SC and metreleptin-treated patients could not be sourced directly from any available data, surrogate data such as HbA1c, ALT and AST were comparatively extensive. Modelling disease progression using a metabolic model allows the use of validated relationships between surrogates and hard outcome to drive transitions through the model – and therefore can reasonably represent the risk of disease progression through worsening organ complications of lipodystrophy. By extending the model to also include a sub-model based on the Markov model observed in the NICE NAFLD guideline (NG49) (25) also allows the key aspects of liver disease progression are captured, which is a major determinant of mortality, costs and quality of life in lipodystrophy patients.

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

Table 38 outlines the assumptions used in the model.

Table 38: Model assumptions

Assumption	Justification
Model structure	
The important costs and consequences can be captured by defining health states as defined in Section 12.1.6	Approach used in the literature and to reflect UK clinical practice.
Disease progression cannot be reversed for cardiovascular, pancreas, kidney, retinopathy, neuropathy sub-models.	Lipodystrophy and the associated complications are progressive.
Patients are able to move from advanced fibrosis to asymptomatic disease in the liver model	In-line with literature and prior NICE NAFLD model (25).
Only first acute event (MI or Stroke) is modelled for the cardiovascular model – a patient cannot experience both	Based on baseline transition probability data available.
Mortality of patients is determined by background general population adjusted for the mortality associated with the health states the patient resides in for each of the Markov models (cardiovascular, kidney, liver and pancreas) for each cycle.	Background mortality reflects baseline mortality risk based on age. There is a greater risk of death associated with certain complications, such as MI or stroke.
Mortality risk within each cycle is equal to all-cause mortality with the mortality risk adjustment for the state with the highest mortality risk out of all the models.	A single highest mortality risk approach was used to estimate each cycles mortality risk. While the literature provides reliable estimates of mortality risk of being in different health states, it is difficult to predict how the different mortality risks are likely to interact with each other in the real world. A conservative approach was therefore taken, by allowing only the state with the highest risk for mortality to inflate the overall risk of mortality in each cycle.
Clinical effectiveness	

The population are reflective of patients with GL or PL lipodystrophy and eligible for treatment (21).	Clinical experts confirmed that the NIH studies 991265/20010769 populations were generalisable to patients seen in clinical practice in England.
All patients with GL have the same disease severity.	Based on natural disease characteristics.
All patients with PL have the same disease severity.	Based on natural disease characteristics.
HbA1c is a robust predictor of disease progression for Cardiovascular, kidney disease, retinopathy, and neuropathy.	Based on Delphi Panel validation (23,62)
Patients discontinue due to non-compliance at a rate of 1.50% for GL patients, and 3.86% for PL patients every cycle.	These values are based on analysis of the NIH studies 991265/20010769 results.
Cost and resource use	
No adverse event costs applied.	There is a minimal impact of these adverse events on costs and QoL, and the difference in the incidence of adverse events between model treatments is also minimal.
Costs attached to the health states in each sub-model are additive within each cycle.	While some of the cycle costs are likely to interact with one another in the model, it was deemed that using the maximum single event cost assumption in a similar fashion to mortality risk would vastly underestimate total costs applied in each cycle (especially considering acute events). Additive costs are therefore the closest estimator of the expected costs.
Quality of life inputs	
No adverse event disutilities applied.	Minimal impact of these adverse events on quality of life and similar in both arms.
Carer disutility was applied in the model for untreated patients.	In line with the recommendations outlined by the NICE HST guidance (123) and what has been accepted by previous NICE HST submissions in similarly devastating rare diseases (120).
Two carers per patient were applied in the model.	Based on the *Lipodystrophy Caregiver Burden Survey* (12).
Carer disutility was applied only to SC-treated patients (and partially – at half magnitude – to patients discontinuing	The burden of patients has been reported as being easier when patients are treated with metreleptin in the *Lipodystrophy Caregiver Burden Survey* (12).

metreleptin, following cessation of treatment)	This is likely due to the impact of lessening symptoms such as hyperphagia, which can have the large impacts on carer welfare (physically and mentally) in the short and long term, as well as better management of the underlying disease and reduction of the risk of complications.
Hyperphagia decrement only applied to SC-treated patients.	Metreleptin treatment significantly decreases satiation time, increases satiety time, decreases energy consumed to produce satiation, and decreases the amount of food desired in the postabsorptive state.
Utility decrements per cycle are calculated multiplicatively.	Aligned with DSU TSD 12 (106).
Abbreviations: DSU, Decision Support Unit; GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; NAFLD, Non-alcoholic fatty liver disease; NIH, National Institute for Health; PL, Partial lipodystrophy; QoL, Quality of life; SC, Supportive care; TSD, Technical Support Document; UK, United Kingdom	

12.1.6 Define what the model's health states are intended to capture.

In the modelling approach adopted (see Section 12.1.3), an individual patient's health is characterised by different health states related to key organ systems such as liver disease, cardiovascular, kidney disease, pancreatitis, retinopathy and neuropathy. Each health state captures the costs and utilities associated with the complications associated with lipodystrophy and reflects the increase in costs and the decline in HRQoL as patients' progress through the disease stages. The various sub-model details are as follows. Information on the factors which drive the transitions in each sub-model is provided in section 12.2.1.

Pancreas sub-model

The pancreas disease Markov sub-model structure aims to capture the onset of pancreatitis due to lipodystrophy. Section 12.1.3 describes the model structure for the pancreas sub-model in more detail.

Liver sub-model

The liver model captures the key stages of liver disease, which is progressive. Patients start in asymptomatic disease, which develops into cirrhosis and further complications such as hepatic cell carcinoma or a transplant. Section 12.1.3. describes the model structure for the liver sub-model in more detail.

Cardiovascular sub-model

The cardiovascular Markov sub-model captures and models the incidence of four cardiovascular complications: angina, CHF, MI and stroke. Section 12.1.3 describes the model structure for the cardiovascular sub-model in more detail.

Kidney sub-model

The kidney disease Markov sub-model structure captures the progression of kidney disease through key health states reflecting severity, which includes microalbuminuria, macroalbuminuria, ESRD, and if necessary, kidney transplant. Section 12.1.3 describes the model structure for the kidney disease sub-model in more detail.

Retinopathy sub-model

The retinopathy disease Markov model structure simulates the transitions of the retinopathy-specific elements of microvascular complications due to lipodystrophy. Section 12.1.3 describes the model structure for the retinopathy sub-model in more detail.

Neuropathy sub-model

The neuropathic disease Markov sub-model structure simulates the transitions of neuropathic and peripheral vascular specific elements of microvascular complications due to lipodystrophy. Section 12.1.3 describes the model structure for the neuropathy sub-model in more detail.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Table 39: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime	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 lifetime, allowing full costs and benefits over the survival time of all patients modelled to be captured.	Section 12.1.3
Discount of 3.5% for costs and benefits	3.5%	NICE reference case	Section 12.1.3
Perspective (NHS/PSS)	UK NHS PSS perspective	NICE reference case	Section 12.1.3
Cycle length	1 year	Aligns with the literature to capture long-term disease progression and follows follow-up time periods for clinical data for metreleptin and SC Half-cycle correction applied.	Section 12.1.3
Abbreviations: 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.

Given the limited availability of data in lipodystrophy, baseline transition probabilities for the liver, cardiovascular, kidney, neuropathy and retinopathy sub-models were obtained from published literature from diseases where lipodystrophy complications are commonly observed. Diabetes-related baseline transition probabilities have been used for the diabetes-related complications, i.e. cardiovascular, kidney disease, neuropathy and retinopathy.

Liver baseline complications have been derived from the NICE NAFLD guideline model.

The transition probabilities for the kidney, neuropathy and retinopathy sub-models were based on the approaches used in the Sheffield Diabetes model. The cardiovascular baseline probabilities were derived from the Diabetes Control and Complications Trial / Epidemiology of Diabetes Interventions and Complications (DCCT / EDIC) study, which reported the overall cardiovascular event rate for 1 year (10.6 events per 1,000 individuals) (124). Data from the Sheffield Diabetes model and DCCT / EDIC study was applied to determine the type of cardiovascular event (i.e. angina, MI, stroke or heart failure) and are summarised in Table 40 below (24,124,125). The probabilities of transitioning to the MI, CHF or stroke health states from angina were assumed to be the same as the probability of transitioning to each of the respective health states from the no CVD state. The remaining transition probabilities for the CVD sub-model were sourced from Smith *et al*. (122), as shown in Table 42.

Table 40: Probability of different cardiovascular events

Cardiovascular event type	Probability of cardiovascular event	Source
MI	0.53	DCCT / EDIC; Sheffield Diabetes model (18,125)
Stroke	0.07	
Angina	0.28	
Heart failure	0.12	
Abbreviations: DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; MI, Myocardial infarction		

The cardiovascular, kidney disease, neuropathy and retinopathy transition probabilities have been adjusted to reflect the lipodystrophy population. This has been done in two ways. Firstly, adjusting the kidney, neuropathy and retinopathy transition probabilities to reflect the baseline HbA1c levels observed in lipodystrophy patients.

The transition probabilities for the kidney, neuropathy and retinopathy from the Sheffield Diabetes model were estimated at a reference HbA1c of 10%. The Eastman's method (126) has been used to adjust relevant transition probabilities to reflect a lipodystrophy patient's baseline HbA1c level using the formula shown in Table 41 below:

$$P_{HbA1c} = P_{HbA1c=10}(HbA1c/10)^{\beta}$$

The baseline probabilities $P_{HbA1c=10}$ were reported in the Sheffield diabetes paper. The equation above adjusts the risk of background retinopathy (10.10), macular oedema (1.20), proliferative retinopathy (6.30), microalbuminuria

(3.25), macroalbuminuria (7.95), and neuropathy (5.30) using the β coefficients reported (shown in brackets) (24).

The second, adjustment is to reflect the risk associated with early-onset type 2 diabetes, which UK clinical experts validated as the closest form of diabetes observed in lipodystrophy patients. The Sheffield diabetes model is for patients with type 1 diabetes. The baseline transition probabilities were therefore adjusted using risk ratios, which were converted from odds ratios, where appropriate (127), for organ-specific complications derived from literature for type 1 versus early-onset type 2 diabetes (128,129). Song has shown that there is a statistically increased risk of cardiovascular and neuropathy events in early-onset type 2 diabetes compared to type 1 diabetes. As such, the odds ratios of 2.04 (p=0.04) and 1.47 (p=0.028) for cardiovascular and neuropathy, respectively, have been applied in the model to reflect the increased risk for lipodystrophy patients (128). The odds ratio for retinopathy complications was not significant (128) ; a mean odds ratio of 1.03 was report (95% confidence interval 0.74 – 1.44; p value not reported). Therefore an adjustment was not applied to the retinopathy sub-model transition probabilities. For the kidney sub-model transition probabilities, a risk adjustment was only applied to transition probabilities for end-stage renal failure (129), as estimates for the relative risk between type 1 vs early-onset type 2 diabetes could not be sourced from literature for the remaining kidney sub-model health states.

To overcome the limited lipodystrophy-specific data available for liver complications, the baseline transitions were utilised from the NICE NAFLD guideline, NG49 (25). The baseline rate of pancreatitis was directly sourced from the GL/PL natural history study (see section 9.8 for further details on this study) (15).

Given that the risk of death was run separate to each of the sub-models, the transition probabilities for the sub-model health states from which patients have a probability of dying were reweighted by dividing by the complement of the probability of mortality for that particular health state.

Table 41: Clinical data used to drive transitions in each of the sub-models

Sub model	Source of baseline model transitions	Outcomes used to drive transition changes	Relative clinical effectiveness between metreleptin and SC approach	Mortality inputs (besides all-cause mortality)
Pancreas	GL/PL Natural History study (15)	Hard outcome – pancreatitis.	ITC	NICE pancreatitis guidance (130)

Liver	NICE NAFLD guideline (25)	Not applicable in the base case. A scenario analysis using ALT and AST (liver enzymes) as surrogates to estimate risk of advanced fibrosis from asymptomatic health state based on risk equation from Houssain *et al.* (131).	Base case: Delphi panel (directly estimated the risk reduction in liver disease complications in metreleptin-treated compared to SC-treated patients). Scenario analysis: Change in ALT and AST from baseline taken from the indirect treatment comparison (see 9.8.1.1.5).	NICE NAFLD guideline (25)
Cardiovascular	DCCT / EDIC study; Sheffield diabetes model (24,124,125) Risk of complications adjusted for relative risk of CVD complications for type 1 diabetes compared to early-onset type 2 diabetes (127,128).	The Delphi panel concluded that HbA1c is a good predictor of CVD outcomes in lipodystrophy patients (23) and relationship with hard outcomes is establish ed. As such, surrogate outcome of HbA1c employed (125,132).	Change in HbA1c from baseline used from NIH studies 991265/200110769 (17); ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data	Smith *et al.* (122)
Kidney	DCCT; Wong *et al.*; UKPDS 33; Sheffield diabetes model; NICE TA358 (24,117,132–134) Risk of complications adjusted for relative risk of ESRD for type 1 diabetes compared to	The Delphi panel concluded that HbA1c is a good predictor of kidney disease outcomes (23) and relationship with hard outcomes is established. As such, surrogate outcome of HbA1c employed (134–136). Adjusted using the Eastman's' method (126).	Change in HbA1c from baseline used from NIH studies 991265/200110769 (17); ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data	Sheffield diabetes model (18)

	early onset type 2 diabetes (129).			
Retinopathy	WESSR XXII, Sheffield diabetes model (24,135)	The Delphi panel conducted concluded that HbA1c is a good predictor of retinopathy outcomes (23) and relationship with hard outcomes is established. As such, surrogate outcome of HbA1c employed (135). Adjusted using the Eastman's' method (126).	Change in HbA1c from baseline used from NIH studies 991265/200110769 (17); ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data	Not applicable.
Neuropathy	DCCT; Moss *et al.;* Sheffield diabetes model (24,136,137) Risk of complications adjusted for relative risk of neuropathy complications for type 1 diabetes compared to early onset type 2 diabetes (127,128).	The Delphi panel conducted concluded that HbA1c is a good predictor of neuropathy outcomes (23) and relationship with hard outcomes is established (134,138,139). As such, surrogate outcome of HbA1c employed. Adjusted using the Eastman's' method (126).	Change in HbA1c from baseline used from NIH studies 991265/200110769 (17); ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data	Not applicable.
Abbreviations: DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; ESRD, End-stage renal disease; GL, Generalised lipodystrophy; HbA1c, Glycated haemoglobin; ITC, Indirect treatment comparison; PL, Partial lipodystrophy; SC, Supportive care				

Annual discontinuation rate for treatment non-compliance from NIH studies 991265/200110769 (1.50% for patients with GL and 3.86% for patients with PL) were employed in the model. Discontinuations due to all reasons observed in the NIH studies 991265/200110769 were not considered to represent that expected to be observed in clinical practice because a number of patients discontinued the studies prematurely to enter the Early Access Programme for metreleptin initiated in the US prior to FDA approval.

Treatment effect

An ITC has been conducted evaluating the clinical effectiveness of metreleptin compared to supportive care using single arm data from the NIH follow-up study and the GL/PL natural history study (15) (see Section 9.8 for further details). It was only feasible to conduct a pooled analysis combining GL and PL patients due the limited sample size of data available with complete data in the GL/PL natural history study. The ITC evaluated and demonstrated statistically and clinically meaningful improvements in HbA1c, liver enzymes (ALT and AST) and pancreatitis differences between patients treated with metreleptin and SC for the pooled lipodystrophy population.

The naïve comparison of the mean HbA1c change of metreleptin compared to supportive care at Month 12 compared to baseline showed an absolute difference of -1.66 (95% confidence interval: -0.90 to -2.35) for the pooled lipodystrophy population (see Table 93). Following the stabilised IPW adjustment used in the ITC, the mean change was -1.52 (95% confidence interval: -0.77 to -2.28). As such, this demonstrated observed reductions NIH studies 991265/200110769 (17) are representative of comparative data for metreleptin in comparison with supportive care.

UK clinical expert opinion indicated that the current estimate of HbA1c reduction from the ITC is an underestimate for patients with GL as it is a pooled analysis. Clinical expert opinion recommends the use of estimates from NIH studies 991265/200110769. As such, the cost-effectiveness analysis models the GL and PL patients separately using this data. The observed mean HbA1c reductions for HbA1c compared to baseline at Month 12 in the NIH studies 991265/200110769 (17) observed was 2.2 and 0.9 for GL and PL patients, respectively. As the ITC results are not available for GL and PL patients separately, these NIH studies 991265/200110769 observed values have been employed in the model. This is considered appropriate given the ITC results have shown that the NIH studies 991265/200110769 HbA1c reductions are representative of comparative data for metreleptin in comparison with supportive care and clinical expert opinion.

The change in HbA1c from baseline between patients treated with metreleptin and SC was used to adjust the baseline transition probabilities to generate probabilities for the metreleptin cohort in the cardiovascular, kidney, neuropathy and retinopathy sub-models. The impact of a reduction of risk of complications in the cardiovascular sub-model is based on data from the UKPDS study (62), a large prospective UK study in patients with type 2 diabetes. This has demonstrated that an absolute reduction of HbA1c per 1%, is associated with a risk reduction of 14%, 12% and 16% for MI, stroke and heart failure, respectively. The relative benefits for kidney, neuropathy and retinopathy

models is driven through the model, as mentioned above, via the application of the Eastman method which modulates the transition probabilities based on HbA1c levels in each cycle (126).

Estimates of benefits for metreleptin-treated patients with respect to liver complications and disease progression compared to patients treated with supportive care were elicited from the Delphi panel in the base case (23). An alternative method estimating the benefit for metreleptin-treated patients using ALT and AST as surrogates is explored in a scenario analysis. This is based on applying the relationship between ALT and AST on predicting the risk of advanced fibrosis in a study by Hossain (131,138). This is described further in section 12.2.3.

Mortality

In order to avoid double counting mortality in each Markov sub-model, the risk of mortality runs separately alongside the various sub-models. All-cause mortality was sourced from UK Life tables available from the Office for National Statistics (139). Risk of mortality is assumed to not fall below that of the UK national life tables as it is assumed that a patient with no complications would have a similar risk of death to that of the general population – i.e. a patient's excess mortality risk is primarily driven by the risk of death associated with the various complications they experience at a particular time point.

States which would inflate the risk of mortality past that of all-cause mortality, and the risk inflation attached to these states, are presented in Table 41. These mortality risk inflators from the separate models are then aggregated using a conservative approach (selecting the highest individual risk of death across all organ systems) to create a single probability for mortality risk. Patients then have a random chance of dying from this mortality risk in any cycle. For a cycle in which a patient dies, the effect of costs and QALYs are reduced by half and reduced to zero from the subsequent cycle onwards.

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?

The clinical benefits observed with metreleptin with respect to HbA1c reduction, liver complications and reduction in the episodes of pancreatitis are sustained in the model while on treatment and partially post discontinuation (HbA1c continues to elevate over the model time horizon as described below. Longer-term data has shown that HbA1c reductions observed with metreleptin have been sustained for at least 48 months. See section 9.6.1 and Figure 15 for further details.

Key baseline characteristics change over time to reflect disease progression and growth as patients develop through childhood to adults. These have been validated with clinical experts and sourced from data previously accepted in NICE appraisals. The changes implemented are as follows:

- HbA1c increase of 0.15% per cycle, as identified from a previous diabetes NICE submission [TA315 (140)]. This is reflective of disease progression observed in diabetes, which is a chronic and progressive condition. The Delphi panel concluded that lipodystrophy patients' HbA1c will plateau over time, identifying a maximum of 12 for poorly controlled patients. This maximum HbA1c level has been implemented in the cost-effectiveness model.

- Weight increases, in different increments between ages 0-9 and 10-18 based on an assumed proportional increase from 0 kg at age 0, to the patient's reported "adult" weight at age 18. The assumed difference in proportional increase is reflective of the difference in proportional weight between children and adolescents. Weight is only used in the when relevant to derive specific dosing requirements in individual patients (i.e. when patients weigh less than 40kg).

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?

HbA1c is used as a surrogate outcome to predict transition probabilities in the cardiovascular, kidney, neuropathy and retinopathy sub-models as outlined in Table 41 and described in section 12.2.1.

For the purpose of validating the use of HbA1c-adjusted transition probabilities from literature, the Delphi Panel was employed to determine the organ-specific aetiology for patients with lipodystrophy. Specifically, to determine whether the cause of key organ-specific complications in lipodystrophy are attributable to:

- Elevated HbA1c

- Elevated TGs

- Other diabetes-related cause (excluding effects of elevated TGs/HbA1c)

- Other lipodystrophy-related cause (excluding effect of elevated TGs/HbA1c and other diabetes-related cause)

- Two or more of the above independently
- None of the above.

The Delphi Panel concluded that HbA1c or co-morbid diabetes is the primary causative factor in the development of cardiovascular, kidney, neuropathy and retinopathy complications in partial and generalised lipodystrophy. For cardiovascular complications, elevated triglycerides were also identified as causative factor. However, due to the lack of data in the literature on the impact of this particular surrogate outcome on cardiovascular events, no adjustment has been taken into account in the transition probabilities and thus, the transition probabilities may be an underestimate of the cardiovascular risk for lipodystrophy patients.

The liver model uses the Delphi panel data which elicited the impact metreleptin has on the reduction of risk on liver complications compared with SC-treated patients (23). A scenario analysis uses changes in ALT and AST to predict adaptions to the transition probabilities between asymptomatic and advanced fibrosis in the liver model, as an alternative to using inputs from the Delphi panel. A risk ratio was calculated using the risk equation in Hossain *et al.* (131) based on change in probability of having advanced fibrosis among patients with type 2 diabetes. The estimated change in ALT and AST level for metreleptin-treated patients compared to those treated with SC from the ITC was used to formulate risk ratios from the Hossain *et al.* regression, which are applied directly to transitions in the liver model.

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.

Adverse events were not included in the cost-effectiveness analysis. Adverse event impacts on costs and utilities were anticipated to have minimal impact on costs as they are mild or moderate in their severity and occur at a low frequency. Adverse events costs and utility impacts related to the specific organ systems included in the Markov sub-models are also already included within the costs and utility decrement estimates present in the model.

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.

Expert opinion was sought to understand the current management of patients with lipodystrophy, key modelling assumptions and model parameters via UK Expert opinion and the Delphi panel.

UK expert opinion has been sought on several occasions in 2019 and 2020 via the three key clinicians at Addenbrooke's Hospital, where the current Early Access Programme operates. The backgrounds for these individuals are:

- Director, [redacted]
- Senior Clinical Fellow, Department of Clinical Biochemistry
- Consultant in Diabetes and Endocrinology.

Furthermore, a Delphi panel was conducted between December 2019 to March 2020 to support the development of the cost-effectiveness model and derive data inputs for the model (23). This involved 10 international key opinion leaders.

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 D5 below.

Clinical transition probabilities are summarised in Table 42, while all other variables are shown in Table 43. For each sub-model, probability of remaining in the same state if allowed is calculated as 1 minus all other probabilities attached to that state.

Table 42: Clinical transition probabilities

Parameters	Transition probability	Source
Liver sub-model – Transition probabilities (unless stated otherwise), per cycle		
Asymptomatic liver disease to Advanced fibrosis	0.0533	NICE NAFLD guideline (25)
Advanced fibrosis to Asymptomatic liver disease	0.1057	
Advanced fibrosis to Compensated cirrhosis	0.0555	
Compensated cirrhosis to Compensated cirrhosis with varices	0.0604	
Compensated cirrhosis to Decompensated cirrhosis	0.0703	
Decompensated cirrhosis to Decompensated cirrhosis with varices	0.1266	
Decompensated cirrhosis to transplant	0.0228	
Compensated cirrhosis with varices to decompensated cirrhosis with varices	0.0703	

Compensated cirrhosis with varices to bleeding	0.1209	
Compensated cirrhosis with varices to HCC	0.0264	
Decompensated cirrhosis with varices to Bleeding	0.3163	
Decompensated cirrhosis with varices to HCC	0.0329	
Decompensated cirrhosis with varices to transplant	0.0228	
Bleeding to decompensated cirrhosis with varices	0.9376	
Bleeding to HCC	0.0369	
Bleeding to transplant	0.0256	
HCC to transplant	0.0408	
Asymptomatic liver disease to Death	0.	
Advanced fibrosis to Death	0.006	
Compensated cirrhosis/ compensated cirrhosis with varices to Death	0.02188	
Decompensated cirrhosis/ decompensated cirrhosis with varices to Death	0.215	
Bleeding to Death	0.2994	
HCC to Death	0.5604	
Transplant to Death	0.181	
Post-transplant to Death	0.0435	
Transplant to Post-transplant	1	Assumption
Risk ratio adjustment 'Asymptomatic liver disease to Advanced fibrosis' transition for SC patients	1.62146	Calculations using Hossain *et al.* (131) and IPW from ITC.
Risk ratio adjustment applied to metreleptin-treated GL patients	0.27	Delphi panel analysis
Risk ratio adjustment applied to metreleptin-treated PL patients	0.75	Delphi panel analysis
Cardiovascular sub-model – Transition probabilities (unless stated otherwise), per cycle		
Post-MI to CHF	0.0224	Smith *et al.* (122)
No CVD to MI	0.0113	Sheffield diabetes model (24), Calculations
No CVD to Angina	0.0060	
No CVD to CHF	0.0026	
No CVD to Stroke	0.0015	
Angina to MI	0.0113	

Angina to CHF	0.0026	Assumption, Sheffield diabetes model (24), Calculations
Angina to stroke	0.0015	
MI to Death	0.0713	Smith *et al.* (122)
Post-MI to Death	0.0286	
CHF to Death	0.43	
Stroke to Death	0.069	
Post-stroke to Death	0.236	
MI risk reduction per 1% reduction in HbA1c	14%	Stratton *et al*. (62)
Stroke risk reduction per 1% reduction in HbA1c	12%	
Heart failure risk reduction per 1% reduction in HbA1c	16%	
OR for CVD complications adjustment for early-onset type 2 diabetes vs compared to type 1 diabetes	2.04	Song *et al.* (128)
Kidney sub-model – Transition probabilities (unless stated otherwise), per cycle		
Healthy to Microalbuminuria	0.0436	Sheffield diabetes model (24)
Healthy to Macroalbuminuria	0.0037	
Healthy to ESRD	0.0008	
Microalbuminuria to macroalbuminuria	0.1565	
Microalbuminuria to ESRD	0.0515	
Macroalbuminuria to ESRD	0.4335	
ESRD to death	0.0884	
Macroalbuminuria to death from ESRD	0.007	
Microalbuminuria to death from ESRD	0.0004	
ESRD to Transplant, 18-34 age	0.152	NICE TA358 (117)
ESRD to Transplant, 35-44 age	0.135	
ESRD to Transplant, 45-54 age	0.114	
ESRD to Transplant, 55-64 age	0.075	
ESRD to Transplant, 65+ age	0.039	
HbA1c adjustment β-coefficient for microalbuminuria	3.25	Sheffield diabetes model (24), see section 12.2.1 for how coefficients used in model.
HbA1c adjustment β-coefficient for macroalbuminuria	7.95	
Early-onset type 2 diabetes relative risk of renal failure compared to type 1 diabetes	4.03	Dart *et al.* (129)
Transplant to Post-transplant	1	Assumption
Pancreatitis sub-model – Transition probabilities (unless stated otherwise), per cycle		
Odds ratio	0.93	ITC analysis (see Section 9.8)

Average events per year (untreated)	[redacted]	Calculation
Average events per year (treated)	[redacted]	Calculation
Neuropathy sub-model – Transition probabilities (unless stated otherwise), per cycle		
Healthy to clinically confirmed neuropathy	0.0512	Sheffield diabetes model (24)
Healthy to pad with amputation	0.0004	
Clinically confirmed neuropathy to pad with amputation	0.0225	
B-coefficient for neuropathy	5.30	Sheffield diabetes model (24), see section 12.2.1 for how coefficients used in model.
OR for neuropathy complications adjustment for early-onset type 2 diabetes compared to type 1 diabetes	1.47	Song *et al.* (128)
Retinopathy sub-model – Transition probabilities (unless stated otherwise), per cycle		
Healthy to Background retinopathy	0.0454	Sheffield diabetes model (24)
Healthy to Proliferative retinopathy	0.0013	
Healthy to Macular oedema	0.0012	
Healthy to Blindness	0.0000019	
Background retinopathy to Proliferative retinopathy	0.0595	
Background retinopathy to Macular oedema	0.0512	
Background retinopathy to Blindness	0.0001	
Proliferative retinopathy to Blindness	0.0038	
Macular oedema to Blindness	0.0016	
β coefficient for Background retinopathy	10.10	Sheffield diabetes model (24), see section 12.2.1 for how coefficients used in model.
β coefficient for Proliferative retinopathy	6.30	
β coefficient for Macular oedema	1.20	
Abbreviations: CVD, Cardiovascular disease; CHF, Congestive heart failure; ESRD, End stage renal disease; HbA1c,Glycated haemoglobin; GL, Generalised lipodystrophy; ITC, Indirect treatment comparison; MI, Myocardial infarction; OR, Odds ratio; PAD, Peripheral arterial disease; PL, Partial lipodystrophy;		

Table 43: Summary of variables applied in cost-effectiveness model

Parameter	Base-case value	Source
Health state utilities		
See section 10.1.9		
Health state costs		
See section 12.3.7		
Patient baseline characteristics		
Mean age, GL male (years)	19.5	NIH studies 991265/20010769 (17)

Mean age, GL female (years)	17.3	
Mean age, PL (years)	37	
Weight, GL male (kg)	55.1	
Weight, GL female (kg)	51.9	
Weight, PL (kg)	68.7	
Weight increase (0-9 years) (kg)	0.061461	
Weight increase (10-18 years) (kg)	0.042821	
HbA1c baseline, GL male	8.1	
HbA1c baseline, GL female	8.8	
HbA1c baseline, PL	8.8	
Number of carers per patient	2	Carer burden survey, calculations
Metreleptin vs. supportive care clinical effectiveness estimates		
HbA1c change with metreleptin, GL	-2.2	NIH studies 991265/20010769 (17) and ITC
HbA1c change with metreleptin, PL	-0.9	NIH studies 991265/20010769 (17) and ITC
Pancreatitis OR for metreleptin vs SC	0.94	ITC
Discontinuation rate		
Discontinuation per cycle	GL: 1.5% PL: 3.86%	NIH studies 991265/20010769 (17)
Abbreviations: HbA1c, Glycated haemoglobin; GL, Generalised lipodystrophy; ITC, Indirect treatment comparison; NIH, National Institutes of Health; OR, Odds ratio; PL, Partial lipodystrophy; SC, Supportive care		

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.

As detailed in Section 8.1.1, NHS England have already established a service specification (A03/S(HSS)/b) which includes the severe lipodystrophies which may be treated with metreleptin for free under an Early Access Programme at Addenbrooke's Hospital This covers both outpatient and, when indicated for initiation of therapy, inpatient. Additional services include diagnostic, therapeutic, and educational support to patients and care givers. Within the context of the overall service specification, only the cost of these additional visits could be considered specific to metreleptin treatment. Diagnostic, dietary, educational and other costs associated with the service specification will be borne regardless, as would expenses associated with therapies other than

metreleptin. 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.

See Section 17.4 (Appendix 4) for details of the updated systematic search of relevant resource data for the NHS in England. Figure 22 in Appendix 5 displays the PRISMA diagram for economic evidence, resource identification and HRQL studies. The previous submission found only studies related to HIV-associated lipodystrophy, which is outside of the scope for the submission, and was therefore not considered relevant resource data.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[3]

Three key steps were taken to ensure the applicability of the resources and costs used in the model for patients with lipodystrophy treated in England.

Firstly, a Delphi Panel including 10 international clinical experts (including 3 of which were clinical experts from Addenbrooke's Hospital), was undertaken to support the re-submission (23). It was necessary to broaden participation to outside of the UK due the rare nature of the condition and limited number of clinical experts residing in the UK. The Delphi Panel focused on determining routine monitoring requirements for patients with lipodystrophy and changes in supportive care medications for patients following the initiation of metreleptin treatment. Many of the participants have experience of using metreleptin via Early Access Programmes or where metreleptin is available via their healthcare system.

Secondly, clinical experts at Addenbrooke's Hospital have been consulted through the development of the *de novo* cost-effectiveness model to validate key data inputs.

Finally, the development of the *de novo* model has relied on existing data and cost-effectiveness analyses developed for NICE appraisals or NICE guidelines.

[3] 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.

As such, many of the values employed in the model from a resource use or cost perspective have been validated in other NICE appraisals or NICE guidelines.

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

There are three presentations available for metreleptin (pack size 30 vials). The list price for metreleptin 11.3 mg (up to a 10 mg dose) injection, 5.8 mg (up to a 5 mg dose) injection, and 3 mg (up to a 2.8 mg dose) injection is £70,050.00, £35,025.00 and £17,512.50, respectively.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

A simple PAS has been approved for metreleptin at a discount of [redacted] of the list price. As such, cost-effectiveness analyses are presented with the PAS discount.

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 and routine monitoring costs. Drug administration costs associated with metreleptin, such as home delivery and self-administration training, are not separately included in this model as these activities will be funded by Amyrt Pharmaceuticals DAC at no additional cost to patients or NHS.

Metreleptin drug costs

In the model, the annual cost of metreleptin is based on a titration phase with all patients initiated on the lowest dose, and therefore using the smallest vial of 3 mg, increasing in a step-wise fashion to the maximum expected distribution of doses based on data from the Early Access Programme at Addenbrooke's Hospital (see Table 44). These data dose was adjusted for potential future increase in dose if such an increase was seen likely in the future, based on the opinions of two clinicians that manage patients with lipodystrophy at Addenbrooke's Hospital. In the model, each titration between vial sizes is anticipated to take place during each of the initial cycles until the maximum expected dose is reached.

The FED (now withdrawn) for the prior metreleptin assessment (1), stated that "the company's estimate of weighted average metreleptin cost was acceptable because it was calculated according to how the drug would be used in clinical practice". The average dose assumption assumes that all patients are in their long-term dose for all time periods and may overestimate costs. As such, the titration has been introduced due to the patient-level nature of de novo model and to reflect the SmPC.

Table 44: Summary of the number of EAP patients currently receiving each metreleptin vial size

	11.3 mg vial (10 mg dose)	5.8 mg vial (5 mg dose)	3 mg vial (2.5 mg dose)
Proportion of EAP patients receiving each vial size	13.0%	60.9%	26.1%
Abbreviations: EAP, Expanded access programme; mg, Milligram; n, Number			

Routine monitoring costs

As described in Section 12.3.3, a Delphi Panel was conducted and routine monitoring requirements were elicited for patients with lipodystrophy. The panel concluded that patients can expect 1 or 2 more visits to a consultant endocrinologist and allied healthcare professionals in the first 12 months following metreleptin initiation, after which no differences are expected in the number of routine monitoring visits between patients receiving metreleptin and those receiving supportive care alone. The UK clinicians participating in the Delphi Panel confirmed that each routine monitoring visit in England involves a joint appointment with a dietician and diabetic nurse alongside an endocrinologist consultant visit. Therefore, the costs of 2 extra visits to an endocrinologist consultant, a dietician and a diabetic nurse in the first 12 months for patients receiving metreleptin, have been included in the model. As such, a patient receiving metreleptin treatment has been assumed to have 3 combined routine monitoring visit in year 1, while a patient receiving supportive care alone has been assumed to have 1 combined routine monitoring visit in year 1.

After year 2, it has been assumed that there are the same routine monitoring requirements for metreleptin, and supportive care alone based on the Delphi

panel findings. This consists of one combined appointment with a dietician and diabetic nurse alongside an endocrinologist consultant visit per year.

The cost of each one combined outpatient appointment is £325.46, based on the individual appointment costs as per the latest published NHS Reference costs, as summarised in

Table 49.

Table 45: Costs per outpatient appointment for routine monitoring of patients with lipodystrophy

Appointment	Cost per visit	Source
Consultant endocrinologist outpatient appointment	£178.06	NHS reference costs 2017/2018, weighted average of service codes: 252 and 302 (consultant) inflated to 2018/2019 using the NHSCII (141,142)
Dietician outpatient appointment	£84.55	NHS reference costs 2017/2018, service code 654 (Total) inflated to 2018/2019 using the NHSCII (141,142)
Diabetic nurse outpatient appointment	£62.85	NHS reference costs 2017/2018, weighted average of currency codes N15AF, N15AN, N1FCF and N15CN inflated to 2018/2019 using the NHSCII (141,142)

Table 46: Total routine monitoring costs for patients with lipodystrophy in year 1 and year 2 onwards

Treatment	Annual routine monitoring costs	
	Year 1	Year 2+
Metreleptin	£ 976.38	£325.46
Supportive care alone	£ 325.46	£325.46

Supportive care alone costs

As described in Section 8, current management of patients in England is based on the use of medications to manage metabolic complications – primarily lipid-lowering therapies and anti-hyperglycaemic medications. The supportive care medication costs are calculated by the use of specific classes of supportive care medications as observed in the NIH studies 991265/20010769 (17) and the drug costs as per the NHS Drug Tariff.

The NIH studies 991265/20010769, classifies supportive care medication as follows:

- Insulin (assumed to be Intermediate or long acting insulin, combined with fast acting insulin in a 70:30 ratio)
- Oral antidiabetic medication: biguanides, thiazolidinediones and sulfonylureas
- Lipid Lowering Therapies: HMG CoA Reductase inhibitors and other lipid modifying agents
- Other concomitant medications: lisinopril and enalapril

The specific medication, form and strength of the medications included in supportive care medications was determined using NHS prescription cost data, 2018 (143), as shown in Appendix 13: Cost effectiveness model. NHS prescription cost data were used to identify the most commonly prescribed medication in each of the medication classes listed above. Furthermore, the strength of the most commonly prescribed medication was assumed to be the daily dose (given this falls within the dose recommended in the BNF (144)). For example, the most commonly prescribed HMG CoA Reductase Inhibitor is atorvastatin 20mg tablets. The BNF recommended dose for atorvastatin is 10–80 mg daily and so it was assumed that the dose of atorvastatin for patients is 20 mg daily. In the case that the strength of the most commonly prescribed medication falls outside the BNF recommended dose, it was assumed that the dose was equal to the starting dose. The dose of insulin (number of units per day) was informed using baseline data from the NIH studies 991265/20010769 (17), as reported by Diker-Cohen *et al.* (74) . The annual cost based on the proportion of patients in each of the subgroups (generalised lipodystrophy or partial lipodystrophy) prescribed each of these medications was then calculated using the NHS drug tariff costs (145). A breakdown of the costs per medication is shown in Appendix 13: Cost effectiveness model.

Metreleptin with supportive care costs

The Delphi Panel agreed that supportive care medications can be discontinued or their dose reduced in some patients with lipodystrophy receiving metreleptin (23).

The model also takes account of the expected reduction in supportive care medication for patients treated with metreleptin. The expected reduction in supportive care medications were informed by the Delphi Panel. The estimates produced during the Delphi Panel are shown below:

Table 47: Expected medication reductions for patients with PL

	Patients able to completely discontinue	**Patients able to reduce dose**	**Anticipated dose reduction for patients able to reduce dose**
Insulin	5%	50%	50%
Oral antidiabetic medication	50% (excluding metformin)	35%	50%
Triglyceride-lowering medication (fibrates)	51%	23%	54%
Antihypertensive medication	14%	10%	31%

Table 48: Expected medication reductions for patients with GL

	Patients able to completely discontinue	**Patients able to reduce dose**	**Anticipated dose reduction for patients able to reduce dose**
Insulin	40%	60%	68%
Oral antidiabetic medication	52% (excluding metformin)	48%	62%

Triglyceride-lowering medication (fibrates)	61%	39%	71%
Antihypertensive medication	17%	12%	32%

These estimates were applied to the baseline supportive care medication costs to determine the expected annual costs for patients being treated with metreleptin, as shown in Appendix 13: Cost effectiveness model.

Summary of drug costs

Table 49 below summarises the drug costs for metreleptin and supportive care employed in the cost-effectiveness model.

Table 49: Drug costs for supportive care

Drug	Annual costs	Source
Supportive care alone medication cost for GL patients	£2,886.00	Based on, NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff (17,143–145)
Supportive care alone medication cost for PL patients	£1,645.61	Based on, NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff (17,143–145)
Supportive care medication cost for patients with GL taking metreleptin	£674.17	Delphi Panel, NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff (17,23,143–145)
Supportive care medication cost for patients with PL taking metreleptin	£1,270.09	Delphi Panel, NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff (17,23,143–145)
Abbreviations: BNF, British National Formulary; PAS, patient access scheme		

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.

As described in Section 12.1, a number of existing NICE-accepted and well established models have been used to inform the design of the model. As such, there are associated cost inputs that have been derived and validated elsewhere. To obtain the health state costs for the model, relevant NICE appraisals and guidelines have been reviewed to obtain the accepted health state values, which has been used in the models.

The primary appraisals and NICE guidelines to obtain health state costs for the sub-models were informed by NICE CG181 (Cardiovascular disease: risk assessment and reduction, including lipid modification), CG182 (Chronic kidney disease in adults: assessment and management), NG17 (Type 1 diabetes: diagnosis and management), TA97 (Dapagliflozin with insulin for treating type 1 diabetes) and NG49 (NAFLD: assessment and management) guidelines (25,114,146,147). Any remaining data gaps were filled from other published sources, namely NHS reference costs, McQueen *et al.* and McEwan *et al.* (141,148,149) All costs were inflated to 2018/2019 values using the NHS Cost

Inflation Index (NHSCII) (142). Any cost values prior to 2014/2015 were first inflated to 2014/2015 values using the PSSRU Hospital & Community Health Services Index and then inflated to 2018/2019 values using the NHSCII (142,150) .

Pancreas

Pancreatitis is an acute event. No prior values were identified in NICE appraisals or guidelines. As such. The cost for an acute pancreatitis event is based on NHS Reference costs using the weighted average cost per finished consultant episode (FCE) of elective inpatients, non-elective long stays, non-elective short stays for endocrine disorders KA08A, KA08B, KA08C.

Liver disease

Annual costs for the liver sub-model were taken with the costs used in the *de novo* cost-effectiveness model developed for the NICE NAFLD guideline (25).

In the NICE NAFLD guideline, the health state costs were calculated based on with the Guideline Development Group (GDG) guidance so they represent a reference patient pathway. The main assumption was that non-NASH patients are managed in primary care while patients with more advanced liver disease are managed in secondary care settings. Health state costs include staff, test, procedure and drug costs where relevant. Staff costs were sourced from the NHS reference cost and PSSRU, and test costs were sourced from Donnan *et*

al. (151). Complication costs related to cirrhosis were sourced from an HTA on HCV patients (152) and were assumed to be relevant to NAFLD patients.

The compensated cirrhosis with varices and decompensated cirrhosis with varices health state costs were assumed to be the same as compensated cirrhosis and decompensated cirrhosis health state costs respectively.

Liver transplant costs were assumed to be similar to those in Hepatitis B or C patients, and were sourced from Brown *et al.* and Wright *et al.* (152,153) .

The 'NAFL-NASH (F012)' and 'Fibrosis F3' costs were assumed to represent the 'asymptomatic liver disease' and 'advanced fibrosis' health states respectively.

Cardiovascular disease

Annual costs for the cardiovascular sub-model were informed using the health state costs in the cost-effectiveness model developed for NICE CG181 (146).

The costs of health states within the evidence base used to inform NICE CG181 were based on estimates of resource use that a typical adult with that cardiovascular condition would be expected to receive in line with NICE guidance and standard NHS practice. Costs were sourced from the NHS Drug Tariff, NHS Reference costs, PSSRU Unit costs of Health & Social Care and the BNF. Standard dosages were also taken from the BNF.

Health state costs in NICE CG181 were presented as 6-monthly costs for event states and annual costs for post-event states. In order to reflect the annual cycle length for our model, half the cost for the post-event state was added to the event state cost from NICE CG181, to obtain annual costs associated with event year states. The stable and unstable angina health states from NICE CG181 were merged into a cost for the angina health state for our model using the prevalence percentage estimate from NG17, based on expert clinical opinion (114).

Kidney disease

The annual costs for microalbuminuria and macroalbuminuria also reflected the approach from NICE TA597 (119). The cost of microalbuminuria was sourced from Thokala *et al.* (24) and includes the cost an annual diagnostic test (test strip) and the cost of angiotensin-converting enzyme (ACE) inhibitor therapy changes. The cost of macroalbuminuria was assumed equal to the cost applied to proteinuria in McQueen *et al.*(148). McQueen *et al.*, obtained this cost by totalling the average inpatient cost for patients with CKD, annual medication

costs comprising losartan, a statin and a beta blocker plus the cost of two outpatient attendances per year.

The annual ESRD health state cost was informed using the 'CKD stage 5' cost from the evidence base which informed NICE CG182 (147). These costs included inpatient stays, nephrology outpatient visits, antihypertensive drugs and GP visits.

The renal transplant and post-renal transplant health state costs were sourced from the evidence base used to inform NG17 (114). The cost of transplantation was obtained from the NHS reference cost code for cadaveric kidney transplant, for both heart beating and non-heart beating donors. The cost of maintenance treatment for transplantation was derived from the cost of immunosuppressive maintenance therapy (154).

Neuropathy and retinopathy

The costing for the neuropathy and retinopathy sub-model health states followed the same approach employed in NICE TA597 (119), with the exception of the 'amputation' health states. Whilst the NICE TA597 model employed separate health states for 'minor amputation' and 'major amputation', our model includes a single 'amputation health state' with cost weighted by the prevalence of minor and major amputations the UK, as reported in the National Diabetes Audit (NDA) 2016-2017 (155). Following the approach reported in McEwan *et al.* (149), NHS reference costs were used to estimate weighted average costs of minor (HRG codes YQ24A–YQ26C) and major (HRG codes YQ21A–YQ22B) amputation. It was assumed that all amputations resulting from neuropathy are elective.

The estimates obtained by McQueen *et al.*(148) for the macular oedema and retinopathy health states were used in the model. These were estimated by costing the resources required within the NICE treatment pathway (114) and applying relevant drug costs, dosing regimens, and staff costs.

Table D8: Health states costs in the cost- effectiveness model

Sub-model / health state	Base-case value, annual cost (2018/2019)	Source
Liver sub-model		
Asymptomatic liver disease	£143.39	NAFL-NASH (F012) cost from NICE NAFLD guideline; PSSRU (25,142)
Advanced fibrosis	£462.28	Fibrosis F3 cost from NICE NAFLD guideline; PSSRU (25,142)
Compensated cirrhosis	£462.28	NICE NAFLD guideline; PSSRU (25,142)
Decompensated cirrhosis	£13,901.68	NICE NAFLD guideline; PSSRU (25,142)
Compensated cirrhosis with varices	£462.28	NICE NAFLD guideline; PSSRU (25,142)
Decompensated cirrhosis with varices	£13,901.68	NICE NAFLD guideline; PSSRU (25,142)
Variceal bleeding (event cost)	£2,839.18	NICE NAFLD guideline; Wright *et al.*; PSSRU (25,142,152)
Hepatocellular carcinoma	£13,901.68	NICE NAFLD guideline; PSSRU (25,142)
Liver transplant (year 1)	£63,295.43	NICE NAFLD guideline; Brown *et al.*; Wright *et al.*; PSSRU (25,142,152,153)
Post liver transplant (year 2)	£19,659.40	NICE NAFLD guideline; Brown *et al.*; Wright *et al.*; PSSRU (25,142,152,153)
Post liver transplant (year 3+)	£8,984.63	NICE NAFLD guideline; Brown *et al.*; Wright *et al.*; PSSRU (25,142,152,153)
CVD sub-model		
Angina (year 1)	£6,854.89	NICE CG181; NICE NG17;PSSRU (114,146)
Angina (year 2+)	£308.55	
Stroke (year 1)	£4,461.79	
Stroke (year 2+)	£165.87	
Congestive heart failure (year 1)	£3,847.55	
Congestive heart failure (year 2+)	£2,779.05	
Myocardial infarction (year 1)	£3,992.55	
Myocardial infarction (year 2+)	£843.24	
Kidney sub-model		
Microalbuminuria	£39.35	NICE TA597; Thokala *et al.*; PSSRU (24,119)
Macroalbuminuria	£4,026.03	NICE TA597; McQueen *et al.*; PSSRU (24,119)
End stage renal disease	£5,632.97	NICE TA358; NICE CG182; PSSRU (117,142,147)
Kidney transplant (year 1)	£22,043.99	NICE NG17; PSSRU (114,142)
Post kidney transplant (year 2+)	£8,233.09	NICE NG17; Wight *et al.*; PSSRU (114,142,154)
Pancreatitis sub-model costs (per-event)		
Acute pancreatitis	£1,174.11	NICE ID861; PSSRU (111,142)
Retinopathy sub-model		
Background retinopathy	£308.42	NICE TA597; NICE NG17; McQueen *et al.*; PSSRU (114,119,148)
Proliferative retinopathy	£1,050.49	
Macular oedema	£3,059.64	

Blindness (year 1)	£5,974.42	NICE TA597; NICE NG17; PSRRU (114,119,142)
Blindness (year 2+)	£5,772.24	
Neuropathy sub-model		
Peripheral neuropathy	£386.81	NICE TA597; NICE NG17; PSSRU (114,119,142)
Amputation (year 1)	£6,090.60	NICE TA597; NHS reference costs 2017/2018; McEwan *et al.*; NDA 2016/2017; PSSRU(119,141,142,149,155)
Amputation (year 2+)	£0	NICE TA597; McEwan *et al.* (119,149)

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.

Adverse event costs were not included because they are anticipated to have minimal impact on costs as they are mild or moderate in their severity and occur at a low frequency.

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.

The model base case does not include costs to caregivers and drug administration costs such as home delivery and self-administration.

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 and fertility complications (females only) and an inability to perform at school or work are not included in the model. This provides additional opportunities for resource saving as hyperphagia, PCOS and an inability to perform at 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. Additionally, metreleptin in children with GL who have not yet developed severe complications of lipodystrophy (uncontrolled diabetes, hypertriglyceridaemia, pancreatitis or steatohepatitis) can prevent these complications (2,156) and provide further opportunities for unquantified health benefits and resource savings.

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.

No structural uncertainties have been explored. The following sensitivity analyses were conducted in the model:

- Deterministic one-way sensitivity analysis (OWSA) on all applicable parameters, using either the upper and lower bounds of 95% confidence intervals, or 20% variation if confidence intervals are unavailable.
- Scenario analyses were conducted to assess the impact of varying inputs in a number of plausible scenarios outlined in Table 50 below.
- Probabilistic sensitivity analysis (PSA). Distributions were selected in line with recommendations made by Briggs *et al.* incorporating uncertainty around parameter estimates into cost-effectiveness modelling (157). PSA was conducted using Monte Carlo simulations to model 100 cohorts of 200 pateints (across 2 treatments and four patient subgroups) encompassing a total of 160,000 patient runs to ensure stable results. A cost-effectiveness acceptability curve (CEAC) was generated through 4,800 patient runs across 43 willingness to pay (WTP) thresholds, totalling 206,400 patient runs to ensure stability.

The following scenarios analyses summarised in Table 50 below were undertaken, with results reported in section 12.5.11.

Table 50: Scenario analysis

Scenario	Scenario description	Justification
A	1.5% discount rate for costs & benefits	Metreleptin delivers long-term health benefits to patients. A discount rate of 1.5% for costs and benefits may be considered relevant where long-term health benefits are likely to be achieved.

Scenario	Scenario description	Justification
B	Liver benefit for metreleptin-treated patients modelled via ALT & AST surrogate outcomes	Relative clinical impact of metreleptin on ALT and AST evaluated in ITC; provides alternative source of benefit on liver outcomes for metreleptin-treated patients.
C	Alternative HbA1c reduction for GL and PL = 1.52%	Directly employing the HbA1c reduction estimated in the indirect treatment comparison. NB. UK clinical expert opinion indicate this is an underestimate for patients with GL as it is a pooled analysis.
D1	Additive disutility calculations per cycle	To provide insight to the change in ICER by using standard utility decrement calculations as opposed to conservative multiplicative utility calculations.
D2	Largest single utility decrement per cycle	To provide insight to the change in ICER by using a more conservative assumption than the present multiplicative utility calculations. Single largest utility decrement can be viewed as the minimum utility decrement to patient utility that is likely to happen.
E	Additive mortality risk inflation	To provide insight into changes in the ICER by using the less conservative assumption of additive mortality risks from different states in the model.
F	Alternative pancreatitis odds ratio of 0.93 between metreleptin and SC, calculated with imputation	To provide insight into changes in the ICER by using alternate methodology in the ITC where missing data was imputed.

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, scenario and probabilistic sensitivity analyses were undertaken, as described above. Standard errors for baseline characteristics are taken

directly from the NIH studies 991265/20010769 report (17). Confidence intervals for the ITC analysis were taken directly from the analysis outputs, and can be found in **Error! Reference source not found.** Variables with an absence of recorded values were varied in the PSA according to an assumed standard deviation of 10%. Values were varied in the OWSA according to a rule of +/- 20%.

Justification for the scenario analyses is given in Table 50.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

All parameters used in the deterministic sensitivity analysis are shown in Appendix 13, section 17.13.2. All parameters used in the probabilistic sensitivity analysis are shown in section 17.13.3.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

The cost of metreleptin remained fixed within the model.

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.

12.5 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 base-case cost-effectiveness results are presented in Table 51 using the approved PASTable 51. Metreleptin accrued [redacted] incremental QALYs and [redacted] incremental costs. This corresponds to an ICER of £179,106 per QALY gained. The ICER has been adjusted according to the NICE HST process guide (123) to reflect the significant QALY gains (>10 incremental undiscounted QALYs) for treated patients, corresponding to an ICER of £151,868. Separate results are also presented for the GL and PL cohorts. These results were based off a cohort of 1000 simulated patients.

Table 51: Base-case results - discounted

Technologies	Total LY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
GL metreleptin	–	[redacted]	8.4	[redacted]	126,044 (adjusted)
PL metreleptin	–	[redacted]	2.16	[redacted]	171,735 (unadjusted)
SC overall	25.31	-	–	-	-
Metreleptin Overall	30.19	[redacted]	4.88	[redacted]	151,868 (weighted average)

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 head-to-head trial of metreleptin compared with supportive care in lipodystrophy patients has been conducted, and therefore this is not possible.

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.

A patient-level model has been used, and therefore this is not appropriate.

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 the model lifetime. The Markov states a patient resides in each of the Markov sub-models in each period generates a QALY decrement that is subtracted from the baseline utilities for SC and Metreleptin-treated patients. QALYs are then summed across all periods in the model, with each period's QALY value discounted appropriately. Since many of the model inputs are probabilistic generated based on plausible distributions, a cohort of 1000 simulated patients was required to ensure robustness around the resulting averaged costs and QALYs.

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:

A patient-level model has been used, and therefore this is not appropriate.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state.

A patient-level model has been used, and therefore this is not appropriate.

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

The undiscounted base-case cost-effectiveness results are presented in Table 52. Metreleptin accrued [redacted] incremental QALYs and [redacted] incremental costs. This corresponds to ICER of £164,291 per QALY gained. Separate results are also presented for the GL and PL cohorts.

Table 52: Undiscounted base-case results

Technologies	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
GL metreleptin	[redacted]	[redacted]	175,389
PL metreleptin	[redacted]	[redacted]	155,754
SC overall	[redacted]	[redacted]	–
Metreleptin overall	[redacted]	[redacted]	164,291

Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in A patient-level model has been used, and therefore this is not appropriate.

12.5.8 .

A patient-level model has been used, and therefore this is not appropriate.

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 Error! Reference source not found.**.**

A patient-level model has been used, and therefore this is not appropriate.

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 55.

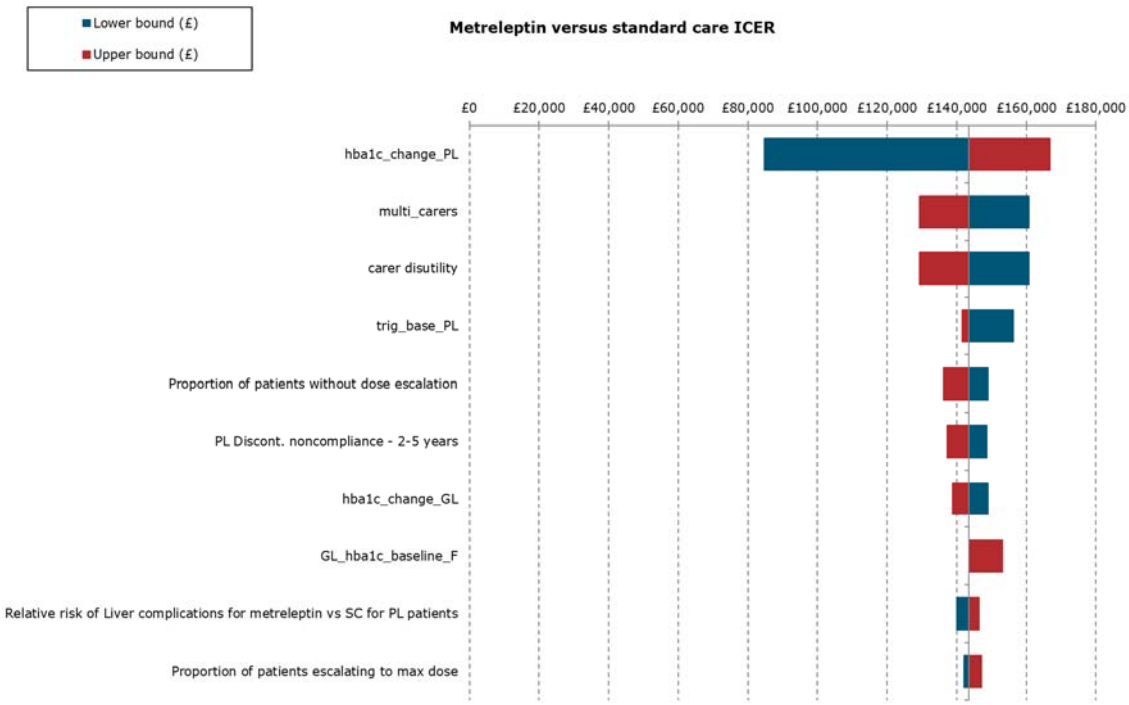
Not applicable.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

The results of the deterministic one-way sensitivity analysis are presented in Figure 30. One-way analyses were conducted by analysing 1 cohort of 200 patients for the base case scenario, and for each of the upper and lower bounds of each parameter. A fixed "seed" of 200 cycles worth of random values was used to ensure comparability of results – ensuring the only variation in values between each 200-patient cohort was the individual corresponding adjusted value.

Figure 30: OWSA ICER results



Results of the scenario analysis outlined in section 12.4.1 are presented in the table below.

Table 53: Scenario analysis results

Scenario	Technologies	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
A (1.5% discount rate)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	170,102

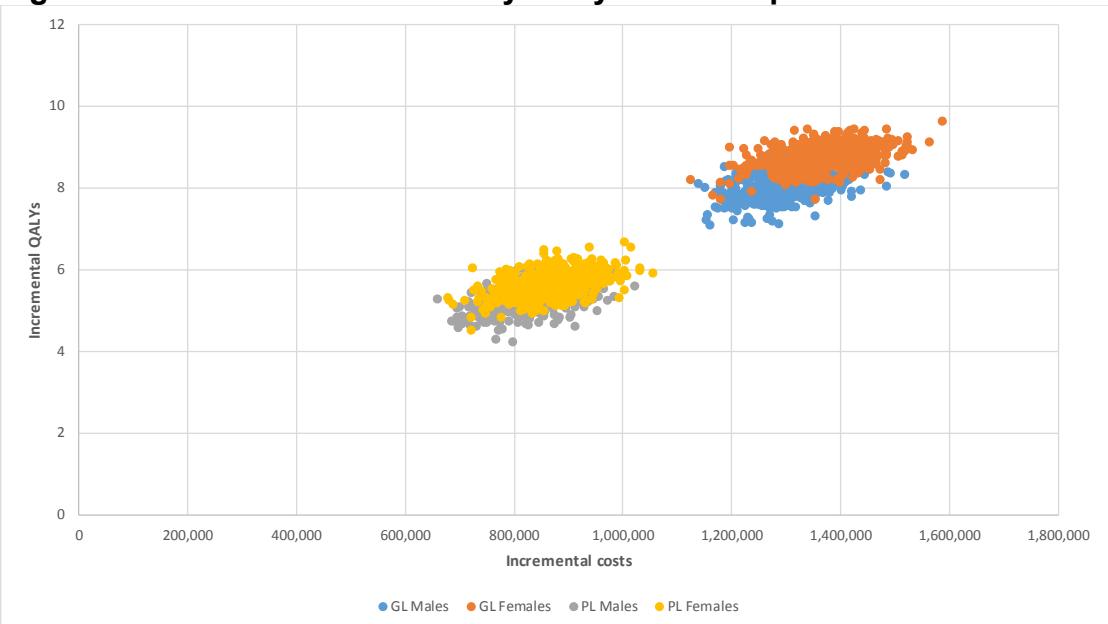
B (ALT / AST surrogate liver outcomes)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	201,395
C (alternative HbA1c reduction: 1.52%)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	194,825
D1 (additive disutility)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	175,758
D2 (largest single utility decrement)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	174,898
E (additive mortality risk inflation)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	180,449
F (pancreatitis benefit, OR = 0.93)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	180,254

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Not applicable.

12.5.12.1 Present results of the probabilistic sensitivity analysis described in table D10.3.

Figure 31: Probabilistic sensitivity analysis scatterplot



Abbreviations: GL – Generalised lipodystrophy; PL – Partial lipodystrophy

Figure 32: Cost-effectiveness acceptability curve

12.5.13 What were the main findings of each of the sensitivity analyses?

Deterministic, probabilistic and scenario analyses demonstrated that the economic results are robust to changes to key model parameters. The key drivers are discussed in section 12.5.14.

One-way analyses showed tight intervals around the base case, with the largest directional change being in the direction of increasing cost-effectiveness.

Probabilistic analyses showed similar robustness of results, with point estimates on a cost effectiveness plane providing a tight spread around all patient subgroups (male and female, GL and PL). Similarly, the cost-effectiveness acceptability curve demonstrated a steep and definitive switch to metreleptin becoming the most likely to be cost-effective from the WTP threshold of £160,000 per QALY gained.

12.5.14 What are the key drivers of the cost results?

The key drivers in the cost-effectiveness model appear to surround HbA1c reductions, and carer disutility settings. For the former, this is likely due to the fact this variable will impact multiple aspects of the model – clinical effectiveness across different organ models, as well as whether patients continue treatment based on the metabolic stopping rule deployed for PL patients. It should be noted that the largest change in the ICER resulted in a decrease to less than £100,000 per QALY gained, due to an increase in the

number of patients stopping treatment; opposing increases were more modest in comparison.

Reducing the carer disutility impacts model results, highlighting the value in the additional information and data gathered from on the burden of lipodystrophy on caregivers as well as their patients.

Miscellaneous results

12.5.15 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

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.

No sub-group analyses have been undertaken, as described in the decision problem table.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-effective ness analysis.

Not applicable.

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

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

There was insufficient clinical data to undertake an ITC for patients with GL or PL, and therefore no further sub-groups have been feasible to include in the cost-effectiveness model.

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 model has been quality checked and validated internally and an external academic modelling expert.

Furthermore, mortality benefits have been validated and compared to existing literature. The life expectancy observed from when patients first enter the model is shown in the figures below. Mean time to death for GL and PL patients has been observed as 51.2 and 66.6 years, respectively, in Akinci *et al.* (15).

Figure 33: Survival of GL, female patients

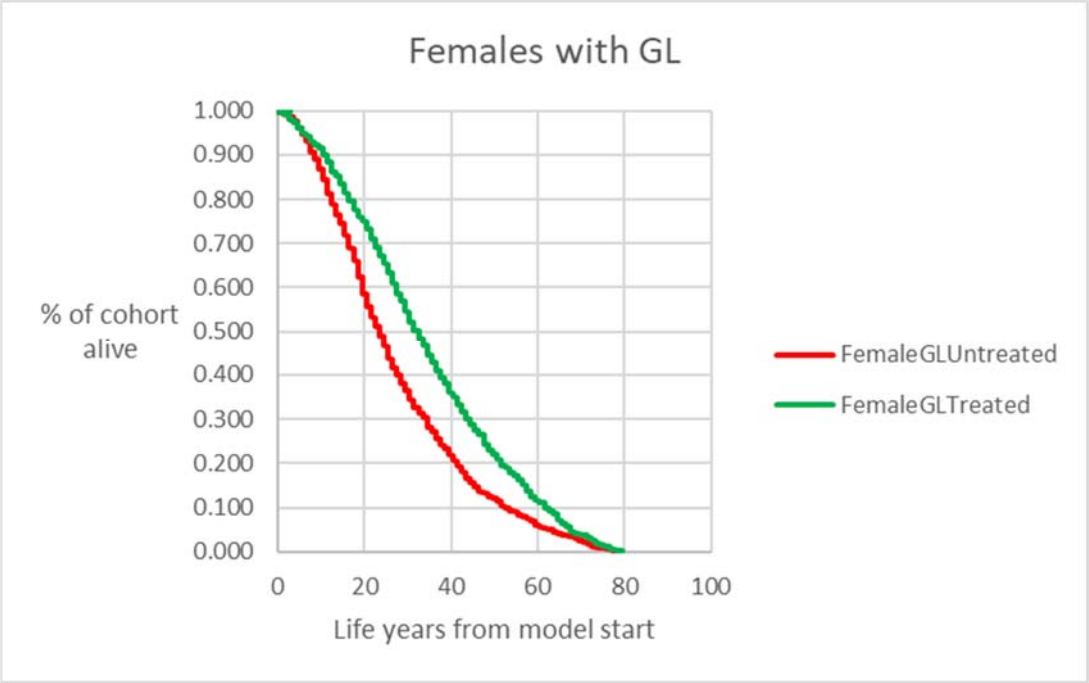


Figure 34: Survival of GL, male patients

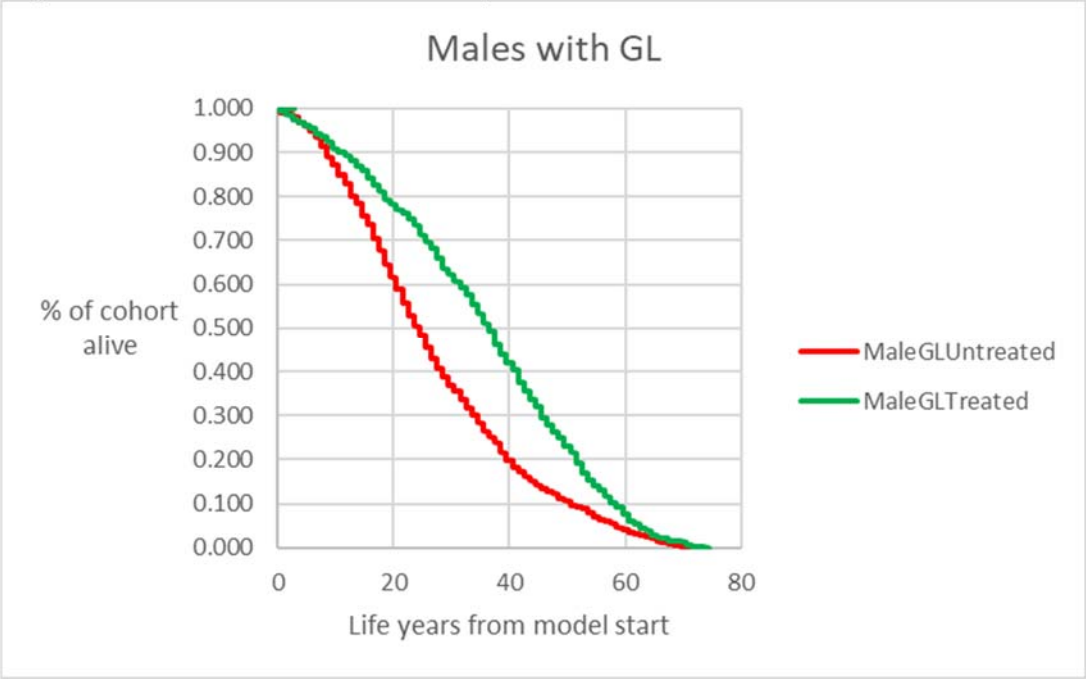


Figure 35: Survival of PL, female patients

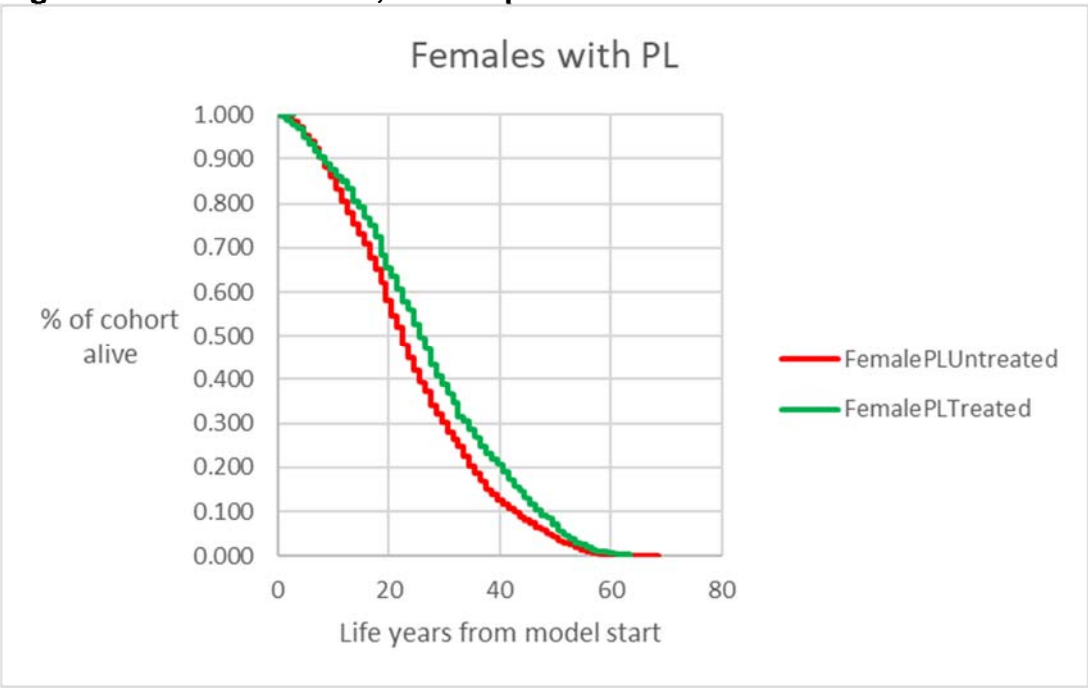
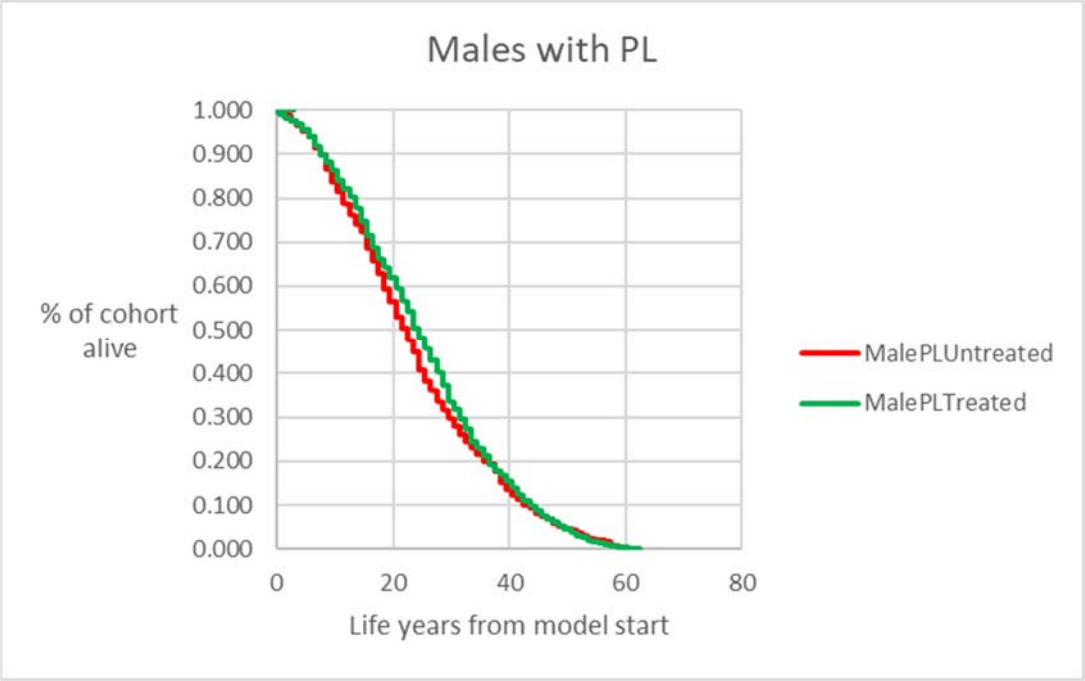


Figure 36: Survival of PL, male patients



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 cost-effectiveness studies comparing metreleptin to supportive care in the UK. As such, it is not possible to comment on the consistency of the current cost-effectiveness analyses compared to published literature.

While two previous cost-effectiveness models have been submitted to NICE as part of this appraisal, the results were not considered robust and therefore have not been compared here.

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?

Yes.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

There are a number of strengths and weaknesses associated the *de novo* cost-effectiveness model.

First, the *de novo* model has addressed the key concerns raised by NICE during the previous steps in the appraisal. A robust ITC has been undertaken (see Section 9.8) to generate clinical effectiveness estimates for metreleptin compared with supportive care using single arm studies. These estimates were all statistically significant except for the all-cause mortality HR and have therefore been employed in the model to drive the benefits associated with metreleptin.

The *de novo* model has been developed incorporating long-term disease progression based on the study population from the pivotal NIH studies 991265/200110769, which clinical experts have validated is generalisable to UK clinical practice (Section 4.3, FED [no withdrawn]).

While there are limited data available for patients with lipodystrophy due the ultra-rare nature of the condition, the *de novo* cost-effectiveness model leverages existing well-established data available in specific complications that are analogous to that observed in patients with lipodystrophy. For example, many patients with lipodystrophy suffer from insulin resistance, leading to diabetes mellitus. The model has utilised robust clinical data from patients with type 1 diabetes and early-onset types 2 diabetes to reflect the baseline transition probabilities for standard of care patients, with respect to diabetes related complications, such as cardiovascular disease, kidney disease and retinopathy. To address remaining data gaps or uncertainties, such as the reduction in supportive care medications for patients using metreleptin or liver outcome benefits, the Delphi Panel was conducted to elicit values amongst 10 of the world's leading international clinical experts in lipodystrophy.

Furthermore, the approach is conservative in many key respects. The Delphi panel has identified the risk factors for many of the complications goes beyond HbA1c and includes triglycerides. The data for risk of complications available in the published literature for diabetes and used in the model captures the association with HbA1c levels, but triglycerides are not reflected in this data and therefore the transition probabilities. As such, the current transition probabilities are expected to be an underestimate where hypertriglyceridaemia contributes to the risk of a complication, such as cardiovascular disease. The other aspect that is conservative is the mortality, where background mortality is used and inflated mortality risk is applied for those severe health states with an increased risk of death. This is a conservative approach, which while minimises the risk

of double counting, results in a likely underestimate of the true mortality benefit associated with metreleptin.

The model uses an efficient and transparent structure for a patient-level model, allowing the model to be evaluated and quality checked more easily than discrete event simulation models. Finally, the model has been validated with clinical experts in the UK.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

None have been identified.

13 Cost to the NHS and Personal Social Services

Summary:
It is estimated that there would be [redacted] patients eligible for treatment with metreleptin in year 1 rising to [redacted] patients in year 5, based on the licenced indication for metreleptin in patients with GL or PL. The estimated uptake rate is 85% in year 1 rising to 90% in year 5. Adherence is assumed as 100%. Annual discontinuation rate comprised of treatment non-compliance from NIH studies 991265/200110769 (1.50% for patients with GL and 3.86% for patients with PL) and stopping rules (0% for patients with GL and 4.54% for patients with PL), which are consistent with the cost-effectiveness analysis. The estimated number of lipodystrophy patients to be treated with metreleptin in England is therefore expected to also rise from [redacted] in year 1 to [redacted] in year 5.

A simple price discount PAS has been approved at [redacted], the corresponding net budget impact of treating the estimated number of patients using all three vial sizes and supportive care, compared with treating only with supportive care is estimated to be [redacted] in Year 1 rising to [redacted] by Year 5. This is based on a 11.3 mg vial (up to a 10 mg dose) cost of [redacted], a 5.8 mg vial (up to a 5 mg dose) cost of [redacted] and a 3 mg (up to a 2.5 mg dose) vial cost of [redacted].

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) identified in the literature search was considered but was not deemed accurate or generalisable for a UK population and the metreleptin licence (34). The study conducted a search of five electronic medical record databases and literature searches to quantitively estimate the prevalence of lipodystrophy 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 lipodystrophy. These study limitations included the search strategy used, the lack of data presented for lipodystrophy subgroups (GL and PL subgroup), 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.

As described in Section 3.4, 8.1.1 and 9 an EAP has been operating for 10 years, offering patients access to metreleptin for free via a single centre at Addenbrooke's Hospital which is part of Cambridge University Hospitals (CUH) NHS Foundation Trust. 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 provided expert opinion to estimate the number of new GL and uncontrolled PL patients, who present each year and would be eligible for metreleptin. Based on expert clinical opinion, it is assumed that [redacted] new patients each year would be eligible for lipodystrophy treatment ([redacted] for GL and [redacted] for PL). From EAP data and expert opinion the expected number of patients eligible over the next 5 years are presented in Table 54.

Table 54: Estimated eligible patient numbers for metreleptin

	Year 1	Year 2	Year 3	Year 4	Year 5
GL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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.

As lipodystrophy patients do not currently have treatments specifically approved for the treatment of lipodystrophy, a high uptake rate for metreleptin following a positive NICE guidance. As metreleptin will no longer be available through the EAP, it is anticipated that the patients currently receiving treatment will continue on metreleptin under the responsibility of the NHS. It is expected that the uptake rate of metreleptin will remain reasonably constant. The uptake rate for metreleptin has been assumed as 85% in year 1 rising to 90% in year 5, based on clinical expert opinion (Table 55). Adherence is assumed as 100%. Annual discontinuation rate comprised of treatment non-compliance from NIH studies 991265/200110769 (1.50% for patients with GL and 3.86% for patients

with PL) and stopping rules (0% for patients with GL and 4.54% for patients with PL), which are consistent with the cost-effectiveness analysis.

Table 55: 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.

According to the Delphi panel conducted, supportive care savings owing to reductions in usage of insulin, oral antidiabetic medication, lipid lowering therapies and antihypertensive medications amount to [redacted] per patient with GL and [redacted] per patient with PL. Furthermore, the Delphi panel also showed that treatment with metreleptin increases disease management costs by [redacted], owing to an increase in outpatient appointments on the first year of treatment; in subsequent years treatment with metreleptin has [redacted] effect on disease management costs versus supportive care.

13.5 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It is not expected that there will be any resource savings, or redirection of resources, which were not possible to quantify.

13.6 Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.

Firstly, 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.

Secondly, the mainstay of support for patients with lipodystrophy involves carers, who are often family members. The negative impact, as described in Section 7.1.4, involves deterioration of mental wellbeing and physical health. In terms of everyday life, it limits their ability to work due to caring responsibilities, reducing their ability to work and work productivity. This societal cost is not captured in the budget impact analysis.

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?

The budget impact with all three vial sizes available is based on the proportion of patients in the EAP data receiving each vial size. The majority of patients (69.23%) receive the 5.8 mg vial with less patients receiving the 11.3 mg vial and 3 mg vial. The proportion of patients receiving each vial size, based on EAP data, is shown in Table 56.

Table 56: Summary of the number of EAP patients currently receiving each vial size

	11.3 mg vial (up to a 10 mg dose)	5.8 mg vial (up to a 5 mg dose)	3 mg vial (up to a 2.5 mg dose)
Proportion of EAP patients receiving each vial size	11.54% (n=[redacted])	69.23% (n=[redacted])	19.23% (n=[redacted])
Abbreviations: EAP, Expanded access programme; mg, Milligram; n, Number			

As noted, there are three vial sizes of metreleptin available (11.3 mg vial, 5.8 mg vial, and 3 mg vial) from Amyrt Pharmaceuticals DAC. The budget impact, with PAS is provided in Table 57. The budget impact considers that 11.54% patients receive the 11.3 mg vial, 69.23% patients receive the 5.8 mg vial, and 19.23% patients receive the 3 mg vial, as per the EAP data. At PAS price, it is estimated that the net budget impact will be [redacted] in Year 1 rising to [redacted] in Year 5.

Table 57: Overall lipodystrophy (GL and PL) budget impact analysis – 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	£1,002	£1,011	£1,024	£1,032	£1,032
Gross medicines costs per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patient numbers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Uptake rate	85%	85%	90%	90%	90%
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other savings / costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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.

Estimating the uptake rate of metreleptin is challenging 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. Furthermore, 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 5-7.5 mg should the patient be prescribed a 5.8 mg vial (up to a 5 mg dose) and 3 mg vial (up to a 2.5 mg dose). 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 lipodystrophy primarily borne by the NHS and PSS. However, the work loss associated with lipodystrophy can be quite substantial. Most patients are affected from birth due to genetic/familial disease, with symptoms manifesting in childhood, and therefore carers/families are also heavily impacted. Lipodystrophy has been found to considerably impact patients' independence and sense of normality in everyday life, including their ability to work and study. 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. While this is an underdeveloped area of research, the costs of reduced productivity at work (due to people with diabetes not working because of death or poor health or working at a lower level of productivity) are estimated at nearly £9 billion (158).

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. Caregivers have to make changes and adjustments to their employment/education due to caring responsibilities (12). 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 lipodystrophy 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 (159). 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.

Costs borne by patients and carers include travel expenses for bi-annual visits to Addenbrooke's Hospital, the only specialist centre in the UK, which can also include overnight accommodation for those travelling further. In addition, other travel costs incurred to local centres post and prior to diagnosis e.g. general practitioner, secondary care.

Furthermore, metreleptin offers the advantage of being administered subcutaneously and therefore can be self-administered avoiding unnecessary travel expenses to the hospital for treatment and any associated carer costs

(including travel or fees for a private carer to escort a patient to the hospital). It also avoids patients and their family members taking unnecessary time off work to attend or escort patients to the appointment.

Other potential costs may include fertility treatment and cosmetic treatment, which are not always reimbursed by the NHS.

14.4 Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.

The *Lipodystrophy caregiver disease burden survey* captured feedback on the burden of disease for caregivers, and resource usage (12). The survey was undertaken in January 2020 via a combination of self-completion questions and a moderator administered 40-minute interview conducted over the telephone with eligible caregivers. The caregivers interviewed were mothers, husbands/partners and daughters of patients. Carers indicated that balancing caring responsibilities alongside other responsibilities can leave the, strained for personal time. In response to the question “Have you had to give up your work/study, reduce your hours, change your type of work/study or retire early due to caring responsibilities?”, 43% of respondents answered “Yes”. Of those who indicated yes, they reported missing 2 to 12 hours of work per week due to caring responsibilities. Balancing carer responsibilities alongside other responsibilities can leave them strained for personal and social time, including time spent with other family members.

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, Amryt Pharmaceuticals has engaged in a comprehensive evidence generation programme to strengthen the evidence base on the understanding of lipodystrophy and the clinical effectiveness of metreleptin. Key recent contributions are outlined in Section 4.1 and includes 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 lipodystrophy patients enrolled in the EAP, including patients treated in England at Addenbrooke’s Hospital
- Characterising the broad and profound impact of metreleptin on lipodystrophy patients beyond HbA1c and triglycerides, but also organ

abnormalities, mortality, hyperphagia, reproductive dysfunction, work/school impact on patients and their carers

Amryt Pharmaceuticals is committed to continue to support such evidence generation, and hopes that based on its reimbursement in the UK, it will be able to continue to support the lipodystrophy community via Addenbrooke's Hospital data collection and ECLip in the future including a more comprehensive review of the burden of disease and performance of metreleptin in UK and other EAP patients via the Addenbrooke's Hospital data collection and ECLip (see Section 4.1).

14.6 Describe the anticipated impact of the technology on innovation in the UK.

Metreleptin is the first and only licensed medicine for the treatment of lipodystrophy which targets the underlying cause of the disease (leptin deficiency) and provides a step-change in the management of this severe debilitating disease. As a result, metreleptin has the potential to dramatically improve patients' lives via slowing disease progression, which has not been achievable before.

The UK is one of the world-leaders for innovation in life sciences, many scientists from other countries come to the UK to research and develop innovative drugs and technologies. To remain world-leaders, it is critical to ensure that these innovative drugs and technologies are adopted for use in the UK as early as possible for the benefit of patients. Positive NICE recommendations for new innovative medicines demonstrate to potential investors that innovative treatments can achieve reimbursement in the UK, allowing the UK to continue to play a leading role at the forefront of medical innovation globally.

Amryt strives to transform the lives of people with rare, debilitating conditions and of those who care for them. However, ground-breaking advances in healthcare such as metreleptin are only meaningful when they reach the people who need them. Reimbursement of metreleptin would enable Amryt to continue to invest in the vital innovation and collaboration required to meet unmet patient and health system needs in the future.

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 EClip registry supports the data collection requirements in relation to the EMA's exceptional circumstances authorisation of metreleptin. The aim of the patient registry is to compile data on the natural history of each different sub-

group of lipodystrophies in patients not exposed to metreleptin, their comorbidities, treatment options used and medical and quality of life out-come for the patients.

In addition, the Addenbrooke's Hospital EAP is reviewing their current approach to data collection and has set-up an enhanced data collection for patients receiving metreleptin from the anticipated date of NICE issuing a positive recommendation for the use of metreleptin in January 2021 (22). Data collection will be enhanced via the introduction of new outcomes and timeframes to be collected including ALT, AST, platelet count and eGFR.

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 Hospital, providing appropriate real-world evidence of relevant outcomes in clinical practice of lipodystrophy patients receiving metreleptin, in order to review its on-going clinical effectiveness. Furthermore, a stopping criteria for metreleptin in PL patients has been applied as part of this appraisal (see section 10.1.16).

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?

No additional infrastructure would be required as metreleptin is administered by the patient or carer after treatment initiation.

Section F - Managed Access Arrangements

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

Not applicable.

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

Not applicable.

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.

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17 Appendices

17.1 Appendix 1: Search strategy for clinical evidence

The following information should be provided:

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.**

For the clinical SLR, the following databases were searched: EMBASE, Medline and Medline® In-process (EMBASE interface 1947 to present) and Cochrane Central Register of Controlled Trials (CENTRAL), hereafter referred to as the Cochrane Library.

The date on which the search was conducted.

16th October 2019

The date span of the search.

For EMBASE, Medline, Medline® In-Process databases search: October 2009 to October 2019, and for Cochrane Central Register of Controlled Trials: February 2017 to October 2019

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).

Table 58: EMBASE, Medline, Medline® In-Process search strategy (EMBASE interface)

Clinical studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Population	('lipodystrophy'/exp OR lipodystrop* OR 'lipid dystroph*' OR lipoatroph*) AND (familial OR inherited OR genetic OR congenital OR partial OR acquired OR generalised OR generalized OR 'fpld*' OR 'cgl*' OR 'agl*' OR 'apl*' OR 'dunnigan adj syndrom*' OR 'lawrence adj syndrom*' OR 'berardinelli* adj syndrom*' OR 'barraquer* adj syndrom*' OR 'wiedemann adj rautenstrauch' OR 'donohue adj syndrom*' OR kobberling OR koebberling OR 'diabetes mellitus'/exp OR 'severe' OR 'insulin resistance'/exp OR 'leptin deficiency'/exp)	7,797
2	Intervention	metreleptin OR myalept* OR leptin	58,159

3	Comparators (Diet and exercise)	‘Exercise’/de OR ‘Physical Education’/de and ‘Training’/de OR ‘Physical Fitness’/de OR ‘Life Style’/de OR ‘Health Education’/de OR ‘Health Behavior’/de OR ‘Health Promotion’/de OR ‘Sports’/de OR ‘Physical Exertion’/de OR ‘Exercise Therapy’/de OR ‘Nutrition Therapy’/de OR ‘Diet Therapy’/de OR ‘Feeding Behavior’/de OR ‘Running’/de OR ‘Diabetic diet’/de OR ‘Jogging’/de OR ‘Swimming’/de OR ‘Walking’/de OR ‘Bicycling’/de OR exercise:ab,ti OR exercising:ab,ti OR exertion*:ab,ti OR sport:ab,ti OR sports:ab,ti OR walking:ab,ti OR jogging:ab,ti OR swimming:ab,ti OR 'strength train*':ab,ti OR 'resistance train*':ab,ti OR 'aerobic train*':ab,ti OR 'physical education*':ab,ti OR 'physical fitness':ab,ti OR nutrition:ab,ti OR nutritional:ab,ti OR 'life style':ab,ti OR lifestyle:ab,ti OR 'health behav*':ab,ti OR 'health educ*':ab,ti OR 'health promot*':ab,ti OR 'physical activit*':ab,ti OR bicycling:ab,ti OR 'weight lift*':ab,ti OR running:ab,ti OR gymnastic*:ab,ti OR dance:ab,ti OR dancing:ab,ti OR diet:ab,ti	1,845,901
4	Comparators (for abnormal physical appearance)	'esthetic surgery'/de OR 'cosmetic surgery':ab,ti OR 'cosmetic techniques':ab,ti OR 'esthetic surgery':ab,ti OR 'surgery, cosmetic':ab,ti OR 'surgery, esthetic':ab,ti	15,487
5	Comparators (for hyperphagia)	'anorexigenic agent'/de OR 'agent, anorexiant':ab,ti OR 'anorectic agent':ab,ti OR 'anorectic drug':ab,ti OR 'anorexant agent':ab,ti OR 'anorexiant':ab,ti OR 'anorexiant agent':ab,ti OR 'anorexiant drug':ab,ti OR 'anorexiants':ab,ti OR 'anorexic agent':ab,ti OR 'anorexic drug':ab,ti OR 'anorexigen':ab,ti OR 'anorexigenic agent':ab,ti OR 'anorexigenic compound':ab,ti OR 'anorexigenic drug':ab,ti OR 'antiappetite agent':ab,ti OR 'appetite depressant agent':ab,ti OR 'appetite depressants':ab,ti OR 'appetite inhibitor':ab,ti OR 'appetite reducer':ab,ti OR 'appetite reducing drug':ab,ti OR 'appetite restrainer':ab,ti OR 'appetite suppressant':ab,ti OR 'appetite suppressing agent':ab,ti OR 'bariatric surgery'/de	34,519

6	Comparators (for insulin resistance and/or diabetes)	'2,4 thiazolidinedione derivative'/de OR '2,4 thiazolidinedione derivative':ab,ti OR 'thiazolidine 2, 4 dione derivative':ab,ti OR 'thiazolidinedione':ab,ti OR 'thiazolidinedione derivative':ab,ti OR thiazolidinediones:ab,ti OR 'metformin'/de OR 'dipeptidyl peptidase iv inhibitor'/de OR 'dpp 4 inhibitor':ab,ti OR 'dpp iv inhibitor':ab,ti OR 'dipeptidyl peptidase 4 inhibitor':ab,ti OR 'dipeptidyl peptidase iv inhibitor':ab,ti OR 'dipeptidyl peptidase iv inhibitors':ab,ti OR 'dipeptidyl-peptidase iv inhibitors':ab,ti OR 'dipeptidylpeptidase 4 inhibitor':ab,ti OR 'dipeptidylpeptidase iv inhibitor':ab,ti OR 'gliptin':ab,ti OR 'gliptins':ab,ti OR 'glucagon like peptide 1 receptor agonist'/de OR 'glp 1 agonist':ab,ti OR 'glp 1 receptor agonist':ab,ti OR 'glucagon like peptide 1 agonist':ab,ti OR 'glucagon like peptide 1 receptor agonist':ab,ti OR 'glucagon like peptide 1 receptor stimulating agent':ab,ti OR 'long acting glp 1 agonist':ab,ti OR 'long acting glp 1 receptor agonist':ab,ti OR 'long acting glucagon like peptide 1 agonist':ab,ti OR 'long acting glucagon like peptide 1 receptor agonist':ab,ti OR 'sodium glucose cotransporter 2 inhibitor'/de OR 'sglt2 inhibitor':ab,ti OR 'sglt2 inhibitors':ab,ti OR 'gliflozin':ab,ti OR 'gliflozin derivative':ab,ti OR 'gliflozins':ab,ti OR 'sodium dependent glucose cotransporter 2 inhibitor':ab,ti OR 'sodium glucose co-transporter 2 inhibitor':ab,ti OR 'sodium glucose cotransporter 2 inhibitor':ab,ti OR 'sodium-glucose transporter 2 inhibitors':ab,ti OR 'insulin'/de OR 'sulfonylurea'/de OR 'sulfonurea':ab,ti OR 'sulfonyl urea':ab,ti OR 'sulfonylcarbamide':ab,ti OR 'sulfonylurea':ab,ti OR 'sulphonurea':ab,ti OR 'sulphonylurea':ab,ti	397,147

7	Comparators (for HTG)	'hydroxymethylglutaryl coenzyme a reductase inhibitor'/de OR ('hmg coa reductase inhibitor':ab,ti OR 'hmg coa reductase inhibitors':ab,ti OR 'hmg coenzyme a reductase inhibitor':ab,ti OR 'hmg-coa reductase inhibitors':ab,ti OR 'hydroxymethylglutaryl coa reductase inhibitors':ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor':ab,ti OR 'hydroxymethylglutaryl-coa reductase inhibitors':ab,ti OR statin:ab,ti) AND drug:ab,ti OR 'statins':ab,ti OR 'vastatin':ab,ti OR 'fibric acid derivative'/de OR 'fibrate':ab,ti OR 'fibrate derivative':ab,ti OR 'fibrates':ab,ti OR 'fibric acid':ab,ti OR 'fibric acid derivative':ab,ti OR 'fibric acid derivatives':ab,ti OR 'fibric acids':ab,ti OR 'fish oil'/de OR 'plasma exchange system'/de OR 'plasma exchange device':ab,ti OR 'plasma exchange system':ab,ti	72,963
8	Comparators (for fatty liver disease)	'cholic acid'/de OR '3, 7, 12 trihydroxycholanic acid':ab,ti OR '3alpha, 7 alpha, 12alpha trihydroxy 5beta cholanic acid':ab,ti OR '3alpha, 7alpha, 12alpha trihydroxy 5beta cholanic acid':ab,ti OR 'chenocholic acid':ab,ti OR 'chobile':ab,ti OR 'cholalic acid':ab,ti OR 'cholate':ab,ti OR 'cholate sodium':ab,ti OR 'cholbam':ab,ti OR 'cholic acid':ab,ti OR 'cholic acid sodium salt':ab,ti OR 'felagol':ab,ti OR 'hydrocholate sodium':ab,ti OR 'kolbam':ab,ti OR 'lipiodol cholic acid salt':ab,ti OR 'nsc 6135':ab,ti OR 'nsc6135':ab,ti OR 'orphacol':ab,ti OR 'sodium cholate':ab,ti OR 'trihydroxycholanic acid':ab,ti OR 'trihydroxycholanoic acid':ab,ti OR 'trihydroxycholic acid':ab,ti	9,693
9	Study types: RCT Filter (https://www.sign.ac.uk/search-filters.html)	('Clinical Trial'/de OR 'Randomized Controlled Trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR Randomization/exp OR 'Single Blind Procedure'/de OR 'Double Blind Procedure'/de OR 'Crossover Procedure'/de OR 'PLACEBO'/de OR 'randomi#ed controlled trial*':ab,ti OR 'rct':ab,ti OR (random* NEXT/2 allocat*):ab,ti OR 'single blind*':ab,ti OR 'double blind*':ab,ti OR ((treble OR triple) NEXT/1 blind*):ab,ti OR 'placebo*':ab,ti OR 'Prospective Study'/de)	2,153,377

10	Observational studies filter (https://www.sign.ac.uk/search-filters.html)	('clinical study'/de OR 'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study or studies)):ti,ab OR ('case control' NEXT/1 (study or studies)):ti,ab OR ('follow up' NEXT/1 (study or studies)):ti,ab OR (observational NEXT/1 (study or studies)):ti,ab OR (epidemiologic* NEXT/1 (study or studies)):ti,ab OR ('cross sectional' NEXT/1 (study or studies)):ti,ab)	3,309,096
11	ERG filter (https://njl-admin.nihr.ac.uk/document/download/20211010)	'incidence' OR 'standardized incidence ratio' OR 'Prevalence' OR 'standardized mortality ratio' OR 'demography' OR 'epidemiological data' OR 'mortality' OR 'disease progression' OR 'disease activity' OR 'morbidity' OR occurrence*:ti,ab,kw OR incidence*:ti,ab,kw OR prevalence*:ti,ab,kw OR episode*:ti,ab,kw OR mortalit*:ti,ab,kw OR morbidit*:ti,ab,kw OR epidemiolog*:ti,ab,kw OR demograph*:ti,ab,kw OR ((natural NEXT/2 history):ti,ab,kw) OR ((disease NEXT/2 progres*):ti,ab,kw) OR ((disease NEXT/2 course):ti,ab,kw) AND [14-10-2009]/sd	2,935,364
12	Combine terms	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) AND (#9 OR #10) OR (#1 AND #11)	1,580

Table 59: Clinical search strategy - Cochrane Central Register of Controlled Trials (Cochrane Library interface)

Clinical, epidemiology, burden of disease and unmet need studies search strategy			
Index	Description	Search terms	Hits
1	Population	MeSH descriptor: [Lipodystrophy] explode all trees OR (lipodystrop* OR lipid dystroph* OR lipoatrophy*) AND (familial OR inherited OR genetic OR congenital OR partial OR acquired OR generalised OR generalized OR 'fpld*' OR 'cgl*' OR 'agl*' OR 'apl*' OR 'dunnigan adj syndrom*' OR 'lawrence adj syndrom*' OR 'berardinelli* adj syndrom*' OR 'barraquer* adj syndrom*' OR kobberling OR koebberling OR 'diabetes mellitus' OR 'severe' OR MeSH descriptor: [insulin resistance] explode all trees OR 'leptin deficiency')	261
2	Combine and date limits	#1 with Cochrane Library publication date from Feb 2017 to Oct 2019	94

Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Supplementary searches of grey literature were performed to identify publications from the past two years and complement the literature database. Sources for these searches included Google Scholar, clinicaltrials.gov, searches of the manufacturer's repository of evidence (including unpublished data and reports), FDA and EMA. In addition, proceedings over the last two years (2018 and 2019) from the following conferences were searched:

- European Association for the Study of Diabetes (EASD)
- European Conference of Endocrinology (ECE)
- European Society for Paediatric Endocrinology (ESPE)
- Paediatric Endocrine Society (PES)

The inclusion and exclusion criteria.

Table 60 - Inclusion and exclusions criteria for published and unpublished studies

Inclusion criteria	
Population	• Adults or children above the age of 2 with generalised lipodystrophy • Adults or children above the age of 12 with partial lipodystrophy[4]
Interventions/Comparators	• Metreleptin • Lifestyle modification: o Diet o Exercise[5] • Cosmetic surgery • Hyperphagia treatment: o Anorexigenic agents o Appetite suppressants o Bariatric surgery • Anti-hyperglycaemic therapy: o Insulin o Thiazolidinediones o Metformin

[4] The partial lipodystrophy patient group is limited to patients for whom standard therapy was not able to provide an adequate metabolic control

[5] It is important to note that there are some lipodystrophy patients who do have a contraindication to exercise

	o DPP-4 inhibitor o GLP-1 agonist o SGLT-2 inhibitor o Sulfonylureas • HTG therapy: o Statins o Fibrates o Fish oil o Thiazolidinediones o Therapeutic plasma exchange • Fatty liver disease therapy: o Cholic acid • Any other interventional therapy for lipodystrophy
Outcomes	• Triglycerides • HbA1c • Pancreatitis • Organ damage • Liver function including cirrhosis • Hyperphagia • Mortality • Adverse events • Pubertal status
Study design	• Randomised controlled trials • Non-randomised controlled trials • Observational studies • Natural history studies
Language restrictions	• None o Papers not available in English assessed on English abstract
Exclusion criteria	
Population	• Studies that do not include patients of interest to the SLR
Interventions/Comparators	• No intervention / comparators of interest
Outcomes	• No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes
Study design	• Individual case study reports • Reviews • Letters • Comment articles
Language restrictions	• Not applicable

The data abstraction strategy.

The relevant data from the included studies were extracted into predefined data extraction tables (DET) by one analyst. All the data points were verified in a quality check of the DET by a second analyst.

Previous SLR findings.

Table 61: Summary of previous SLR references with reasons for exclusion

Reference	Publication	Included?	Reason for exclusion
Original SLR			
Oral *et al.* 2002	Leptin-replacement therapy for lipodystrophy	Yes	
Javor *et al*. 2005	Long-term efficacy of leptin replacement in patients with generalized lipodystrophy.	Yes	
Javor *et al.* 2005	Leptin reverses nonalcoholic steatohepatitis in patients with severe lipodystrophy.	No	Secondary publication
Petersen *et al.* 2002	Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy	No	Secondary publication
Oral *et al*. 2006	Leptin replacement therapy modulates circulating lymphocyte subsets and cytokine responsiveness in severe lipodystrophy.	No	Secondary publication
Moran *et al.* 2004	Changes in Body Composition in Patients with Severe Lipodystrophy after Leptin Replacement Therapy.	No	Outcome
Musso *et al.* 2005	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	No	Secondary publication
Park *et al.* 2007	Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy	Yes	
Chan *et al.* 2011	Clinical effects of long-term metreleptin treatment in patients with lipodystrophy	No	Duplicate

Joseph *et al*. 2014	Lipid regulation in lipodystrophy versus the obesity-associated metabolic syndrome: The dissociation of HDL-C and triglycerides.	No	Conference – not in date
Christensen *et al*. 2014	Bone mineral content in patients with congenital generalized lipodystrophy is unaffected by metreleptin replacement therapy.	No	Secondary publication
Chong *et al*. 2009	Efficacy of leptin therapy in the different forms of human lipodystrophy	Yes	
Brown *et al.* 2013	Metreleptin treatment for metabolic abnormalities associated with lipodystrophy: Achieving A1C and triglyceride targets.	No	Conference – not in date
Muniyappa *et al.* 2014	Effects of leptin replacement therapy on pancreatic beta-cell function in patients with lipodystrophy	Yes	
Diker-Cohen *et al*. 2015	Partial and generalized lipodystrophy: Comparison of baseline characteristics and response to metreleptin	Yes	
Ajluni *et al.* 2016	Efficacy and Safety of Metreleptin in Patients with Partial Lipodystrophy: Lessons from an Expanded Access Program.	No	Secondary publication
Safar Zadeh *et al*. 2013	The liver diseases of lipodystrophy: The long-term effect of leptin treatment.	Yes	
Beltrand *et al*. 2007	Metabolic correction induced by leptin replacement treatment in young children with Berardinelli-Seip congenital lipoatrophy.	Yes	
Beltrand e*t al*. 2010	Resistance to leptin-replacement therapy in Berardinelli-Seip congenital lipodystrophy: An immunological origin	Yes	
Simha *et al*. 2012	Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the dunnigan variety.	Yes	
Araujo-Vilar *et al.* 2015	Recombinant human leptin treatment in genetic lipodystrophic syndromes: the long-term Spanish experience.	Yes	

Asthana *et al.* 2015	Effects of recombinant human leptin (metreleptin) therapy on plasma angiopoietin-like proteins 3 and 4 in lipodystrophy patients	Yes	
Brown *et al.* 2015	Effects of leptin on glucose and lipid metabolism during constant food intake.	No	Conference – not in date
Ebihara *et al*. 2007	Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy	Yes	
Schlogl *et al*. 2016	Leptin substitution in patients with lipodystrophy: Neural correlates for long-term success in the normalization of eating behavior	Yes	
Vatier *et al* 2016	One-year metreleptin improves insulin secretion in patients with diabetes linked to genetic lipodystrophic syndromes	Yes	
Dantas de Medeiros Rocha *et al.* 2010	Effect of diet intervention and oral zinc supplementation on metabolic control in Berardinelli-Seip syndrome	No	Population
Updated SLR			
Abel *et al*. 2016	Hypercortisolemia in patients with non-HIV associated lipodystrophy.	No	Outcome
Ahmad *et al.* 2013	Cholic acid for hepatic steatosis in patients with lipodystrophy: a randomized, controlled trial.	Yes	
Ajluni *et al*. 2015	Metreleptin in patients with partial lipodystrophy	No	Conference – not in date
Ajluni *et al.* 2017	Efficacy of metreleptin therapy in the treatment of fatty liver disease associated with partial lipodystrophy.	No	Conference not included in search
Ajluni *et al.* 2017	Metreleptin effects on mixed-meal response in partial lipodystrophy	Yes	
Araujo *et al.* 2015	Berardinelli Seip syndrome. Analysis of clinical cases. Atherosclerosis	Yes	

Arioglu *et al*. 2000	Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes.	No	
Brown *et al.* 2017	Effects of metreleptin in pediatric patients with lipodystrophy	Yes	
Brown *et al*. 2016	Recombinant methionyl human leptin (Metreleptin) improves glucose and lipid metabolism during constant food intake in humans	No	Conference – not in date
Brown *et al.* 2018	Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy.	Yes	
Kassai *et al.* 2016	Effect of leptin administration on circulating apolipoprotein CIII levels in patients with lipodystrophy	Yes	
Lightbourne *et al.* 2017	Effects of leptin on regulators of lipoprotein lipase in patients with lipodystrophy	Yes	
Lima *et al*. 2017	Early results of the first Brazilian patients with generalised congenital lipodystrophy on treatment with metreleptin	Yes	
Lungu *et al.* 2012	Insulin resistance is a sufficient basis for hyperandrogenism in lipodystrophic women with polycystic ovarian syndrome.	Yes	
Meral *et al*. 2018	Clinical predictors of leptin response for improvement in liver histopathology in a cohort of patients with partial lipodystrophy.	Yes	
Muniyappa *et al.* 2017	Metreleptin therapy lowers plasma angiopoietin-like protein 3 in patients with generalized lipodystrophy.	Yes	
Oral *et al.* 2017	Impact of metreleptin on hepatomegaly in patients with generalised lipodystrophy.	Yes	
Papendieck *et al.* 2018	Clinical outcome in a series of pediatric patients with congenital generalized lipodystrophies treated with dietary therapy.	Yes	
Parsloe *et al.* 2015	Effects of weight change on metabolic outcomes in patients with lipodystrophy attending the national severe insulin resistance service	No	Conference – not in date

17.1.1 Second Pass Exclusions

Table 62: Second Pass References Excluded

Year	Author(s)	Title	Journal	Reason?
2013	Ahmad Z.; Subramanyam L.; Szczepaniak L.; Simha V.; Adams-Huet B.; Garg A.	Cholic acid for hepatic steatosis in patients with lipodystrophy: A randomized, controlled trial	European Journal of Endocrinology	Outcome
2017	Ajluni N.; Meral R.; Neidert A.H.; Rus D.; Hench R.; Conjeevaram H.; Oral E.A.	Metreleptin effects on mixed-meal response in partial lipodystrophy	Diabetes	Outcome
2015	Akinci B.; Koseoglu F.; Onay H.; Yavuz S.; Altay C.; Simsir I.; Ozisik S.; Demir L.; Korkut M.; Yilmaz N.; Ozen S.; Akinci G.; Atik T.; Calan M.; Secil M.; Comlekci A.; Demir T.	Acquired partial lipodystrophy is associated with increased risk for metabolic complications	Endocrine Reviews	Outcome
2018	Akinci B.; Oral E.; Neidert A.; Rus D.; Cheng W.Y.; Thompson-Leduc P.; Salinardi T.; Cochran E.; Brown R.J.	Burden of illness associated with generalized lipodystrophy in leptin replacement therapy-naïve patients: A longitudinal medical chart review study	Endocrine Reviews	Duplication
2017	Akinci G.; Topaloglu H.; Demir T.; Danyeli A.E.; Talim B.; Keskin F.E.; Kadioglu P.; Talip E.; Altay C.; Yaylali G.F.; Bilen H.; Nur B.; Demir L.; Onay H.; Akinci B.	Clinical spectra of neuromuscular manifestations in patients with lipodystrophy: A multicenter study	Neuromuscular Disorders	Outcome
2017	Akinci G.; Topaloglu H.; Demir T.; Danyeli A.E.; Talim B.; Keskin F.E.; Kadioglu P.; Talip E.; Altay C.; Yaylali G.F.; Bilen H.; Nur B.; Demir L.; Onay H.; Akinci B.	Clinical spectra of neuromuscular manifestations in patients with lipodystrophy: A multicenter study	European Journal of Paediatric Neurology	Duplication
2018	Ali O.A.; Cook K.; Gupta D.; Holmqvist D.; Lee D.; Ng C.K.; Bradt P.; Brown R.	Effect of leptin replacement therapy (LRT) on survival and disease progression in generalized and partial lipodystrophy (GL, PL)	Diabetes	Study type
2015	Araujo M.; Papendiek L.	Berardinelli Seip syndrome. Analysis of clinical cases	Atherosclerosis	Outcome
2014	Ayad M.; Zaakouk A.; El-Mougi M.	Epidemiology of lipohypertophy versus lipoatrophy among type1 diabetic school children in Menofia, Egypt	Pediatric Diabetes	Outcome

2007	Beltrand J.; Beregszaszi M.; Chevenne D.; Sebag G.; De Kerdanet M.; Huet F.; Polak M.; Tubiana-Rufi N.; Lacombe D.; De Paoli A.M.; Levy-Marchal C.	Metabolic correction induced by leptin replacement treatment in young children with Berardinelli-Seip congenital lipoatrophy	Pediatrics	Outcome
2018	Brown R.J.; Brychta R.; Startzell M.; Chen K.; Marshall B.; Christensen J.; Meehan C.; Valencia A.; Gorden P.	Leptin replacement does not increase energy expenditure in leptin-deficient patients with lipodystrophy	Endocrine Reviews	Outcome
2017	Brown R.J.; Meehan C.A.; Cochran E.; Rother K.I.; Kleiner D.E.; Walter M.; Gorden P.	Effects of metreleptin in pediatric patients with lipodystrophy	Journal of Clinical Endocrinology and Metabolism	Outcome
2015	Chan J.L.; Koda J.; Heilig J.; Cochran E.; Gorden P.; Oral E.A.; Brown R.J.	Immunogenicity associated with metreleptin treatment in patients with obesity or with lipodystrophy	Endocrine Reviews	Study type
2018	Cook K.; Ali O.; Gupta D.; Holmqvist D.; Lee D.; Ng C.; Bradt P.; Brown R.	Effect of leptin replacement therapy (LRT) on survival and disease progression in generalised and partial lipodystrophy (GL, PL)	Diabetologia	Outcome
2018	Cook K.; Stears A.; Araujo-Vilar D.; Santini F.; O'Rahilly S.; Ceccarini G.; Frois C.; Bradt P.; Savage D.	REAL-WORLD EXPERIENCE OF GENERALIZED LIPODYSTROPHY PATIENTS ENROLLED IN THE METRELEPTIN EARLY ACCESS PROGRAM: INITIAL RESULTS	Value in Health	Study type
2017	De Franca L.C.; Dias M.A.; Neto J.M.; Valerio C.	Evaluation of the presence of steatosis and fibrosis in lipodystrophic with diabetes type 2 patients using transient elastography and comparison with antropometric and densitometric parameters	Hepatology	Outcome
2010	Do Rêgo A.G.; Mesquita E.T.; De Faria C.A.; Do Rêgo M.Á.G.; Baracho M.D.F.P.; Santos M.G.D.N.; Do Egito E.S.T.; Neto J.B.	Cardiometabolic abnormalities in patients with berardinelli-seip syndrome	Arquivos Brasileiros de Cardiologia	Outcome
2010	Ebihara K.; Kusakabe T.; Aotani D.; YujiYamamoto; Yamamoto S.; Masuzaki H.; Hosoda K.; Nakao K.	Lipodystrophy and leptin-replacement therapy in Japan	Journal of Molecular Neuroscience	Study type
2018	Eldin A.J.; Meral R.; Neidert A.H.; Rus D.; Hench R.; Oral H.; Oral E.A.	ECG and echo characteristics in familial partial lipodystrophy: The impact of Lamin A variants	Journal of Clinical and Translational Science	Outcome

2018	Eldin A.J.; Meral R.; Neidert A.H.; Rus D.; Hench R.; Oral H.; Oral E.A.	ECG and echo characteristics in familial partial lipodystrophy: The impact of Lamin A variants	Journal of Clinical and Translational Science	Outcome
	EUCTR2017-003014-22-AT	Leptin in hepatic lipid metabolism in humans		Outcome
2018	Fernandes V.O.; Liberato C.B.R.; Olegario N.B.C.; Montenegro A.D.R.; Paiva G.E.C.; Batista L.A.A.; Martins L.V.; Liberato I.L.R.; Carvalho A.B.; D'Alva C.B.; Montenegro Junior R.M.	Subclinical ventricular dysfunction in young population with congenital generalised lipodystrophy detected by speckle-tracking echocardiography	Diabetologia	Outcome
2018	Fernandes V.O.; Ponte C.M.M.; Gurgel M.H.C.; Montenegro A.P.D.R.; Batista L.A.A.; Liberato C.B.R.; D'alva C.B.; Montenegro R.M.	Insulin resistance, cardiovascular autonomic neuropathy, and left ventricular hypertrophy in patients with congenital generalized lipodystrophy	Diabetes	Outcome
2011	Foss-Freitas M.C.; Monteiro L.Z.; Coeli F.B.; Pereira F.A.; Montenegro Junior R.M.; Foss M.C.	Metabolic profile in women with Dunnigan-type partial familial lipodystrophy caused by R482W mutation in the LMNA gene	Diabetologia	Outcome
2017	Garnica-Cruz P.; Orozco-Covarrubias L.; De Ocariz M.S.; Duran-McKinster C.; Palacios-Lopez C.; Garcia-Romero M.T.	Acquired localized lipoatrophies in children: A retrospective study of 12 patients and review of the literature	Pediatric Dermatology	Outcome
2009	Guedes Do Rego A.; Faria C.; Tinoco Mesquita E.; Sobral- Filho D.; Silveira Moraes R.; Guedes Do Rego M.; Tabosa Do Egito E.; Brandao Neto J.	Metabolic syndrome, an important issue in patients with congenital generalized lipodystrophy	European Heart Journal	Outcome
2005	Javor E.D.; Cochran E.K.; Musso C.; Young J.R.; DePaoli A.M.; Gorden P.	Long-term efficacy of leptin replacement in patients with generalized lipodystrophy	Diabetes	Outcome
2017	Jeru I.; Vatier C.; Vantyghem M.-C.; Lascols O.; Vigouroux C.	LMNA-associated partial lipodystrophy: Anticipation of metabolic complications	Journal of Medical Genetics	Outcome
2018	Kushchayeva Y.; Kushchayev S.; Lightbourne M.; Skarulis M.; Brown R.	Thyroid abnormalities in patients with severe insulin resistance syndromes: Does leptin treatment play a role?	Thyroid	Outcome

2018	Lightbourne M.; Brown R.J.; Startzell M.	Treatment of metabolic complications in patients with partial lipodystrophy using volanesorsen, an antisense oligonucleotide to apolipoprotein ciii	Endocrine Reviews	Intervention
2018	Lightbourne, M; Brown, RJ; Startzell, M	Treatment of metabolic complications in patients with partial lipodystrophy using volanesorsen, an antisense oligonucleotide to apolipoprotein ciii	Endocrine reviews	Study type
2017	Lima J.G.; Lima N.N.; Santos M.C.F.; Vieira T.C.; Silva P.H.D.; Nobrega L.H.C.; Baracho M.F.P.; Jeronimo S.M.B.	Early results of the first Brazilian patients with generalised congenital lipodystrophy on treatment with metreleptin	Diabetologia	Population
2018	Malandrino N.; Reynolds J.; Brychta R.J.; Chen K.; Gharib A.M.; Walter P.J.; Garraffo H.M.; Startzell M.; Cochran E.K.; Gorden P.; Brown R.J.	Measurement of visceral fat by dual-energy x-ray absorptiometry and absence of correlation with metabolic parameters in lipodystrophy	Endocrine Reviews	Outcome
2018	Melvin A.; Adams C.; Flanagan C.; Gaff L.; Jenkins-Liu C.; Withers E.; O'Rahilly S.; Savage D.B.; Williams R.; Stears A.	Audit of five-year outcomes from the National Severe Insulin Resistance Service	Diabetic Medicine	Outcome
2016	Miehle K.; Ebert T.; Kralisch S.; Hoffmann A.; Kratzsch J.; Schlögl H.; Stumvoll M.; Fasshauer M.	Serum concentrations of fibroblast growth factor 21 are elevated in patients with congenital or acquired lipodystrophy	Cytokine	Outcome
2017	Montenegro R.; Fernanades V.; Salinardi T.; Heideier C.; Montenegro A.; Ponte C.; Vasconcelos I.; Karbage L.; Fernandes P.; Carvalho A.; De Araújo Batista L.; Lima L.; Liberato C.; D'Alva C.	Severe metabolic abnormalities observed in patients with confirmed diagnosis of congenital generalized lipodystrophy including AGPAT2 and BSCL2 mutations	Journal of Inborn Errors of Metabolism and Screening	Outcome
2004	Moran S.A.; Patten N.; Young J.R.; Cochran E.; Sebring N.; Reynolds J.; Premkumar A.; Depaoli A.M.; Skarulis M.C.; Oral E.A.; Gorden P.	Changes in Body Composition in Patients with Severe Lipodystrophy after Leptin Replacement Therapy	Metabolism: Clinical and Experimental	Outcome
2017	Muniyappa R.; Abel B.S.; Asthana A.; Walter M.F.; Cochran E.K.; Remaley A.T.; Skarulis M.C.; Gorden P.; Brown R.J.	Metreleptin therapy lowers plasma angiopoietin-like protein 3 in patients with generalized lipodystrophy	Journal of Clinical Lipidology	Outcome

2014	Muniyappa R.; Brown R.J.; Mari A.; Joseph J.; Warren M.A.; Cochran E.K.; Skarulis M.C.; Gorden P.	Effects of leptin replacement therapy on pancreatic β-cell function in patients with lipodystrophy	Diabetes Care	Outcome
2014	NCT00360139	Clinical Trial to Determine the Efficacy of Sculptra™ Dermal Filler for the Correction of Contour Deformities Caused by Lipoatrophy	https://clinicaltrials.gov/show/NCT00360139	Outcome
2006	NCT00457639	Cholic Acid for Hepatic Steatosis in Lipodystrophy		Outcome
	NCT00457938	Novel Therapies for Metabolic Complications of Lipodystrophies		Outcome
	NCT01511016	Leptin for Abnormal Lipid Kinetics in HIV Lipodystrophy Syndrome	https://clinicaltrials.gov/show/NCT01511016	Population
2012	NCT02430077	Phase 2 Study of Obeticholic Acid for Lipodystrophy Patients		Outcome
	NCT02527343	The BROADEN Study: a Study of Volanesorsen (Formerly ISIS-APOCIIIRx) in Patients With Familial Partial Lipodystrophy	https://clinicaltrials.gov/show/NCT02527343	Intervention
2015	NCT02639286	Efficacy, Safety and Tolerability of ISIS 304801 in People With Partial Lipodystrophy With an Open-Label Extension		Intervention
	Niinikoski H.; Näntö-Salonen K.; Ruusu P.; Kinnala A.; Putto-Laurila A.; Toppari J.; Keskinen P.	Insulin-induced lipoatrophy in children	Duodecim; lääketieteellinen aikakauskirja	Outcome
2010	Oral E.A.; Araujo-Vilar D.; Brown K.; Brown R.J.; Garg A.; Isupov T.; Jae D.H.P.; Miller V.R.; Savage D.B.; Stratton A.	Lipodystrophy connect: The global registry	Endocrine Reviews	Outcome
2015	Oral E.A.; Chiquette E.; Lewis J.H.; Long A.; Salinardi T.; Brown R.	Impact of metreleptin on hepatomegaly in patients with generalised lipodystrophy	Diabetologia	Duplication
2017	Parente E.B.; Simoes V.R.F.; Medeiros M.A.; Bacha I.E.; Parisi E.R.; Salles J.E.N.	SGLT2 inhibitors effect on fatty liver disease in patients with Berardinelli-Seip lipodystrophy	Diabetologia	Outcome
2018	Park J.Y.; Javor E.D.; Cochran E.K.; DePaoli A.M.; Gorden P.	Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy	Metabolism: Clinical and Experimental	Outcome

2007	Ponte C.M.M.; Fernandes V.O.; Gurgel M.H.C.; Vasconcelos I.T.G.F.; Karbage L.B.A.S.; Liberato C.B.R.; Negrato C.A.; Gomes M.B.; Montenegro A.P.D.R.; Montenegro Júnior R.M.	Early commitment of cardiovascular autonomic modulation in Brazilian patients with congenital generalized lipodystrophy	BMC Cardiovascular Disorders	Outcome
2018	Ponte C.M.M.; Fernandes V.O.; Liberato C.B.R.; Montenegro A.P.D.R.; Batista L.A.; Gurgel M.H.C.; De Azevedo Karbage L.B.; Vasconcelos I.T.G.F.; D'Alva C.B.; Montenegro Júnior R.M.	Association between cardiovascular autonomic neuropathy and left ventricular hypertrophy in young patients with congenital generalized lipodystrophy	Diabetology and Metabolic Syndrome	Outcome
2019	Resende A.T.P.; Martins C.S.; Bueno A.C.; Moreira A.C.; Foss-Freitas M.C.; De Castro M.	Phenotypic diversity and glucocorticoid sensitivity in patients with familial partial lipodystrophy type 2	Endocrine Reviews	Study type
2018	Schmidt F.; Kapellen T.M.; Wiegand S.; Herbst A.; Wolf J.; Fröhlich-Reiterer E.E.; Rabl W.; Rohrer T.; Holl R.W.	Diabetes mellitus in children and adolescents with genetic syndromes	Experimental and Clinical Endocrinology and Diabetes	Study type
2012	Simha V.; Subramanyam L.; Szczepaniak L.; Quittner C.; Adams-Huet B.; Snell P.; Garg A.	Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the dunnigan variety	Journal of Clinical Endocrinology and Metabolism	Outcome
2012	Simha V.; Szczepaniak L.S.; Wagner A.J.; Depaoli A.M.; Garg A.	Effect of leptin replacement on intrahepatic and intramyocellular lipid content in patients with generalized lipodystrophy	Diabetes Care	Outcome
2003	Volkova N.I.; Davidenko I.Y.	Clinical significance of lipohypertrophy without visual and palpable changes detected by ultrasonography of subcutaneous fat	Terapevticheskii arkhiv	Population
2019	Zadeh E.S.; Lungu A.O.; Cochran E.K.; Ghany M.G.; Heller T.; Kleiner D.E.; Gorden P.	The metabolic liver disease of lipodystrophy: The effect of leptin treatment	Diabetes	Outcome

17.2 Appendix 2: Search strategy for adverse events

Adverse events were included as an outcome of interest in the selection criteria for clinical evidence in Appendix 1, see Table 60.

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.**

For the economic evidence SLR, the following databases were searched: EMBASE, Medline and Medline® In-process (EMBASE interface 1947 to present), Centre for Reviews and Dissemination (CRD) HTA and NHS Economic Evaluation Database (EED), and the EuroQol database.

17.3.2 The date on which the search was conducted.

16th October 2019

17.3.3 **The date span of the search**.

2006 to 16th October 2019

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).

Table 63: Economic evidence search strategy

Economic evaluations, utility, and cost and resource use studies search strategy			
Index	**Description**	**Search terms**	**Hits**

13	Economic Filter (https://www.sign.ac.uk/search-filters.html)	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost* AND [1-2-2017]/sd	137,293
14	Health state utility values filter (http://www.yhec.co.uk/yhec-content/uploads/2015/06/Poster-374-Sensitivity-Of-A-Search-Filter.pdf)	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti AND [1-2-2017]/sd	211,987

15	Resource use filter	(burden OR resource*):ti OR (burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti OR (resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti OR 'office visits':ab,ti OR 'ambulatory care'/de OR (visit OR visits OR visited):ab,ti OR appointment*:ab,ti OR hospitalization/de OR (hospitalization* OR hospitalisation* OR hospitalised OR hospitalized):ab,ti OR (admission* OR readmission* OR admitted OR readmitted):ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR (bed NEXT/3 day*):ab,ti OR ((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti OR ((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti OR ((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti AND [1-2-2017]/sd	378,687
16	Combine terms	#1 AND (#13 OR #14 OR #15)	122
17	Combine terms	#12 OR #16	1,605

Table 64: Economic evidence search strategy - Cochrane Central Register of Controlled Trials (Cochrane Library interface)

Clinical, epidemiology, burden of disease and unmet need studies search strategy			
Index	Description	Search terms	Hits
1	Population	MeSH descriptor: [Lipodystrophy] explode all trees OR (lipodystrop* OR lipid dystroph* OR lipoatrophy*) AND (familial OR inherited OR genetic OR congenital OR partial OR acquired OR generalised OR generalized OR 'fpld*' OR 'cgl*' OR 'agl*' OR 'apl*' OR 'dunnigan adj syndrom*' OR 'lawrence adj syndrom*' OR 'berardinelli* adj syndrom*' OR 'barraquer* adj syndrom*' OR kobberling OR koebberling OR 'diabetes mellitus' OR 'severe' OR MeSH descriptor: [insulin resistance] explode all trees OR 'leptin deficiency')	261
2	Combine and date limits	#1 with Cochrane Library publication date from Feb 2017 to Oct 2019	94

17.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Supplementary searches of grey literature were performed to complement the database searches for quality of life studies. The following sources were searched for English language materials:

- HTA websites: NICE; Pharmaceutical Benefits Scheme (PBS); Canadian Agency for Drugs and Technologies in Health (CADTH); Scottish Medicines Consortium (SMC), The National Healthcare Institute in the Netherlands (ZiN); Institute for Quality and Efficiency in Healthcare (IQWiG) and Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) in Germany; Belgium Healthcare Knowledge Centre; Autoridade Nacional do Medicamento e Produtos de Saúde I. P. (Infarmed) in Portugal; Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) in Spain; Generalitat de Catalunya (GENCAT) in the Catalan region of Spain; Haute Autorité de Santé (HAS) in France.
- Google Scholar
- Relevant conference proceedings from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) EU, International Conference on Metabolic Syndrome, International Conference on Endocrinology.

17.3.6 The inclusion and exclusion criteria

Table 65: The inclusion and exclusion criteria for economic evidence

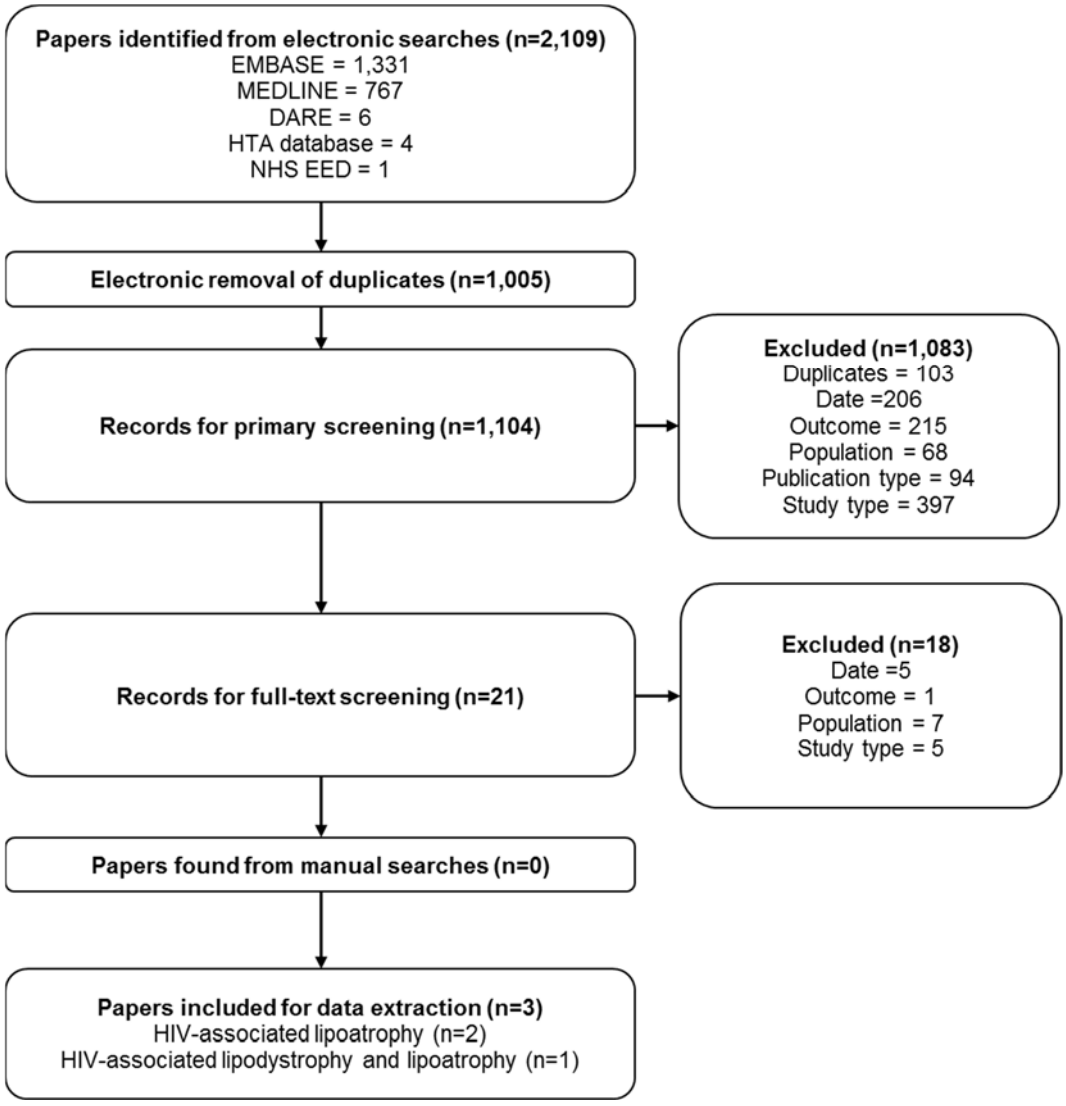
Inclusion criteria	
Population	• Adults or children with generalised lipodystrophy • Adults or children with partial lipodystrophy • Patients with rare lipodystrophy syndromes e.g. Donohue syndrome and Wiedemann Rautenstrauch syndrome
Interventions	• No restriction by intervention or comparator
Outcomes	• Cost per physical unit gained/avoided • Cost per QALY gained • Net monetary benefit • Incremental costs
Study design	• Economic evaluations: o Cost-effectiveness analysis o Cost-utility analysis o Cost-benefit analysis o Cost-minimisation analysis Economic evaluation alongside clinical trials (EEACT)
Language restrictions	• None o Papers not available in English assessed on English abstract
Search dates	March 2017 to October 2019
Exclusion criteria	
Population	• Studies that do not include patients of interest to the SLR
Interventions	• None
Outcomes	• No reported outcomes of interest
Study design	• Cost study • Burden of disease study • Resource use study • Reviews • Letters • Comment articles • Individual case study reports
Language restrictions	• Not applicable
Search dates	March 2017 to October 2019

17.3.7 The data abstraction strategy.

The relevant data from the included studies were extracted into predefined data extraction tables (DET) by one analyst. All the data points were verified in a quality check of the DET by a second analyst

17.3.8 Previous submission economic evidence PRISMA

Figure 37: Previous submission PRSIMA diagram to show the identification of economic evaluations associated with lipodystrophy



17.4 Appendix 4: Resource identification, measurement and valuation

The following information should be provided.

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.)

17.4.1 The date on which the search was conducted.

16th October 2019

17.4.2 The date span of the search.

2006 to 16th October 2019

17.4.3 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.)

17.4.4 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Details for any additional searches for resource identification, measurement and valuation is the same as for economic evidence (Section 17.3.)

17.4.5 **The inclusion and exclusion criteria**.

Table 66: Inclusion and exclusion criteria for resource identification, valuation and measurement studies

Inclusion criteria

Population	• Adults or children with generalised lipodystrophy • Adults or children with partial lipodystrophy • Patients with rare lipodystrophy syndromes e.g. Donohue syndrome and Wiedemann Rautenstrauch syndrome
Interventions/Comparators	• No restriction by intervention or comparator
Outcomes	• Unit costs • Resource use • Budget impact • Cost of illness
Study design	• Cost study • Burden of disease study • Resource use study • Economic evaluations: • Cost-effectiveness analysis • Cost-utility analysis • Cost-benefit analysis • Cost-minimisation analysis • EEACT
Language restrictions	• None • Papers not available in English assessed on English abstract
Search dates	• March 2017 (original SLR) and October 2019 (updated SLR)
Exclusion criteria	
Population	• None
Interventions/Comparators	• No intervention / comparators of interest
Outcomes	• No reported outcomes of interest
Study design	• Reviews • Letters • Comment articles • Individual case study reports
Language restrictions	• Not applicable
Search dates	2006 (original SLR) to January 2017, and January 2017 to October 2019 (updated SLR)

Abbreviations: EEACT – Economic evaluation alongside clinical trials; SLR – Systematic literature review

17.4.6 The data abstraction strategy.

The relevant data from the included studies were extracted into predefined data extraction tables (DET) by one analyst. All the data points were verified in a quality check of the DET by a second analyst.

17.5 Appendix 5: Search strategy for HRQL evidence

The following information should be provided.

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.**

The search strategy for HRQL is the same as for economic evidence (Section 17.3.)

The date on which the search was conducted.

16th October 2019

The date span of the search.

2006 to 16th October 2019

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 HRQL is the same as for economic evidence (Section 17.3.)

Details of any additional searches (for example, searches of company databases [include a description of each database]).

Details for any additional searched for HRQL is the same as for economic evidence (Section 17.3.)

17.5.1 The inclusion and exclusion criteria.

Table 67: Selection criteria used for published HRQL studies

Inclusion criteria	
Population	• Adults or children with generalised lipodystrophy • Adults or children with partial lipodystrophy

	• Patients with rare lipodystrophy syndromes e.g. Donohue syndrome and Wiedemann Rautenstrauch syndrome
Interventions/Comparators	• No restriction by intervention or comparator
Outcomes	• Utility scores • Disutilities
Study design	• Randomised controlled trials • Non-randomised controlled trials • Observational studies • HRQL elicitation studies • HRQL validation studies • Economic evaluations: o Cost-utility analysis • EEACT
Language restrictions	• None o Papers not available in English assessed on English abstract
Search dates	March 2017 (original SLR) and October 2019 (updated SLR)
Exclusion criteria	
Population	• None
Interventions/Comparators	• No intervention / comparators of interest
Outcomes	• Quality-of-life measures that are not on reported on scale of 0-1
Study design	• Reviews • Letters • Comment articles • Individual case study reports
Language restrictions	• Not applicable
Search dates	2006 (original SLR) to January 2017, and January 2017 to October 2019 (updated SLR)

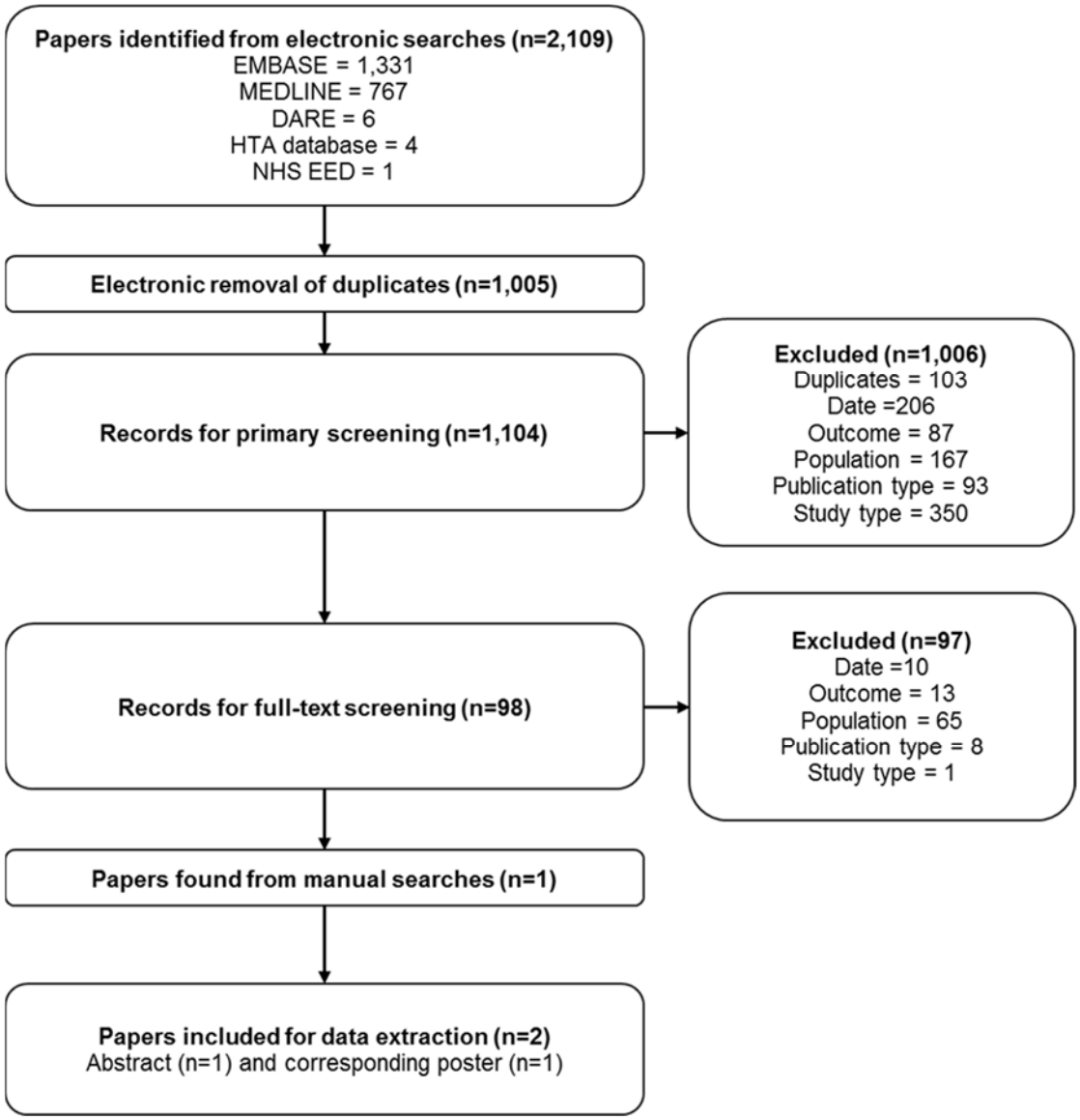
Abbreviations: EEACT – Economic evaluation alongside clinical trials; HRQL – Health-related quality-of-life; HTG – Hypertriglyceridaemia; SLR – Systematic literature review

The data abstraction strategy.

The relevant data from the included studies were extracted into predefined data extraction tables (DET) by one analyst. All the data points were verified in a quality check of the DET by a second analyst.

17.5.2 Previous submission HRQL PRISMA

Figure 38: Previous submission PRISMA diagram to show the identification of HRQL associated with lipodystrophy



17.6 Appendix 6: List of studies

17.6.1 Published studies

Metreleptin Studies

A total of 38 studies were identified, all of which evaluated metreleptin as an intervention within a lipodystrophy patient sample. Eighteen of the studies refer to a clinical trial(s). The details are these studies are described in Table 68 - Table 80.

Table 68: Metreleptin Study Results: NCT01679197

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Ajluni *et al.* 2017b(160) *Abstract*	Prospective open-label, Single arm	PL 78% Female Age (yrs): 12-64	14	12	2.5-10 mg/d	Fasting TG (primary), HbA1c

PL – Partial lipodystrophy; PPARG; TG – Triglycerides; Yrs – Years

Table 69: Metreleptin Study Results: NCT00025883

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Abel *et al.* 2016(71) *Full Article*	Prospective non-randomised	AGL, CGL, FPLD (Treated, Naïve) 66% Female	12	0.63*	10 mg/d	TG, HbA1c
Brown *et al.* 2017(72) *Full Article*	Prospective open-label, Single arm	AGL, CGL, FPL, Atypical Progeria 77% Female Age(yrs): 12.8±4.4†	53	12±0.2	12 months: 0.082±0.028† After 12 months: 0.11±0.04†	HbA1c (primary), AST (primary), ALT (primary), TG
Brown *et al.* 2018(20) *Full Article*	Open-label	AGL, CGL	66	36	0.10	Fasting TG (primary), HbA1c (primary), Fasting leptin, ALT, AST
Chong *et al.* 2010(73) *Full Article*	Prospective open-label	LD	48	12	0.04–0.24	HbA1c (primary)
Diker-Cohen *et al*. 2015(74) *Full Article*	Prospective open-label, Single arm	GL, PL	86	12-108	0.06–0.24	TG , HbA1c (primary), Leptin

Kassai *et al.* 2016(75) *Full Article*	Prospective open-label	LD Controls	LD:114 Controls:60	6–12	0.04–0.16	TG, HbA1c, Plasma leptin
Lee *et al*. 2019(49) *Full Article*	Open-label	GL, PL 83% Female	115	24	1-2 times daily	TG, HbA1c, Leptin
Muniyappa *et al*. 2014(76) *Full Article*	Prospective open-label	AGL, APL, CGL, FPLD 77% Female Age (yrs):8-54	13	4-5	4-5 months: 4.19±1.87mg/d†	TG, HbA1c, Leptin,
Muniyappa *et al*. 2017(77) *Full Article*	Prospective open-label	GL, Controls	GL:22 Controls:39	4-8	0.07±0.02†	TG, HbA1c, ALT, AST
Oral *et al.* 2017a(46) *Abstract*	Prospective open-label	GL 67% Female Age (yrs): 24±16†	21	12		TG (primary), HbA1c (primary), ALT (primary), AST (primary)
Oral *et al.* 2017b(78) *Poster*	Prospective open-label	GL 67% Female Age (yrs): 17 (median), 8-68	21	12	1-2 times daily	Fasting TG (primary), HbA1c (primary), ALT (primary), AST (primary)
Sekizkardes *et al*. 2019(79) *Full Article*	Prospective open-label, Single arm	FPLD (PPARG, LMNA)	PPARG:7 LMNA:22	12	0.08–0.16	TG, HbA1c (primary), ALT, AST, Serum leptin

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; APL – Acquired partial lipodystrophy; BMI – Body mass index; BSCL – Berardinelli-seip congenital lipodystrophy; CGL – Congenital generalised Lipodystrophy; CPL – Congenital Partial Lipodystrophy; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; SD – Standard deviation; Total Cholesterol; TG – Triglycerides; Yrs – years

Table 70: Metreleptin Study Results: NCT01778556

Primary study reference (Full or abstract)	**S-udy design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Abel *et al.* 2016(71) *Full Article*	Prospective non-randomised	AGL, CGL, FPLD (Treated, Naïve) 66% Female	12	0.63*	10 mg/d	TG, HbA1c
Brown *et al.* 2017(72) *Full Article*	Prospective open-label, Single arm	AGL, CGL, FPLD, Atypical Progeria 41% Female Age (yrs): 12.8±4.4†	53	12±0.2	12 months: 0.082±0.028† After 12 months: 0.11±0.04†	HbA1c (primary), AST (primary), ALT (primary), TG
Lee *et al.* 2019(49) *Full Article*	Open-label	GL, PL 83% Female	115	24	1-2 times daily	TG, HbA1c, Leptin

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; CGL – Congenital generalised Lipodystroph ; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystroph; SD – Standard deviation; TG – Triglycerides; Yrs – years

Table 71: Metreleptin Study Results: NCT00005905

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Brown *et al.* 2017(72) *Full Article*	Prospective open-label, Single arm	AGL, CGL, FPLD, Atypical Progeria 41% Female Age (yrs): 12.8±4.4†	53	12±0.2	12 months: 0.082±0.028† After 12 months: 0.11±0.04†	HbA1c (primary), AST (primary), ALT (primary)
Brown *et al.* 2018(20) *Full Article*	Open-label	AGL, CGL	66	36	0.10	Fasting TG (primary), HbA1c (primary), Fasting leptin, ALT, AST
Lee *et al.* 2019(49) *Full Article*	Open-label	GL, PL 83% Female	115	24	1-2 times daily	TG, HbA1c, Leptin

Sekizkardes *et al.* 2019(79) *Full Article*	Prospective open-label, Single arm	FPLD (PPARG, LMNA)	PPARG:7 LMNA:22	12	0.08–0.16	TG, HbA1c (primary), ALT, AST, Serum leptin

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; BMI – Body mass index; CGL – Congenital generalised Lipodystrophy; CPL – Congenital Partial Lipodystrophy; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; SD – Standard deviation; Total Cholesterol; TG – Triglycerides; Yrs – years

Table 72: Metreleptin Study Results: NCT02262806

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Brown *et al.* 2017(72) *Full Article*	Prospective open-label, Single arm	AGL, CGL, FPLD, Atypical Progeria 41% Female Age (yrs): 12.8±4.4†	53	12±0.2	12 months: 0.082±0.028† After 12 months: 0.11±0.04†	HbA1c (primary), AST (primary), ALT (primary), TG
Sekizkardes *et al.* 2019(79) *Full Article*	Prospective open-label, Single arm	FPLD (PPARG, LMNA)	PPARG:7 LMNA:22	12	0.08–0.16	TG, HbA1c (primary), ALT, AST, Serum leptin

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; BMI – Body mass index; CGL – Congenital generalised Lipodystrophy; CPL – Congenital Partial Lipodystrophy; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; SD – Standard deviation; TC: Total Cholesterol; TG – Triglycerides; Yrs – years

Table 73: Metreleptin Study Results: NCT02262832

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Brown *et al.* 2017(72) *Full Article*	Prospective open-label, Single arm	AGL, CGL, FPLD, Atypical Progeria 41% Female Age (yrs): 12.8±4.4†	53	12±0.2	12 months: 0.082±0.028† After 12 months: 0.11±0.04†	HbA1c (primary), AST (primary), ALT (primary), TG

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; CGL – Congenital generalised Lipodystrophy; CPL – Congenital Partial Lipodystrophy; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; PL – Partial lipodystrophy; SD – Standard deviation; TG – Triglycerides; Yrs – years

Table 74: Metreleptin Study Results: NCT00677313

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Zadeh *et al.* 2013(65) *Full Article*	Prospective open-label, Single arm	AGL, APL, CGL, FPLD	27	Mean: 25.8 Range:4-68	0.06–0.24	Fasting TG, HbA1c, Serum leptin, ALT, AST

†Mean±SD *Assuming 30 days in a month

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; APL – Acquired partial lipodystrophy; CGL – Congenital generalised Lipodystrophy; FPLD – Familial partial lipodystrophy; SD – Standard deviation; TG: Triglycerides

Table 75: Metreleptin Study Results: NCT00001987

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Kassai *et al.* 2016(75) *Full Article*	Prospective open-label	LD, Controls	LD:60 Controls:54	6-12	0.04–0.16	TG, HbA1c, Plasma leptin

†Mean±SD
Lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; SD – Standard deviation; TG – Triglycerides

Table 76: Metreleptin Study Results: NCT00457938

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Simha *et al.* 2012(161) *Full Article*	Parallel group open-label observational Phase 2/3	FPLD (MH,SH) 100% Female	24	6	0.08	Fasting TG (primary), HbA1c, ALT, AST

†Mean±SD
ALT – Alanine transaminase; AST – Aspartate transaminase; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; SD – Standard deviation; TC – Total cholesterol; TG – Triglycerides

Table 77: Metreleptin Study Results: NIH991265

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Oral *et al.* 2002(69) *Full Article*	Prospective open-label, Single arm	AGL, CGL, FPLD 100% Female Age (yrs): 15-42	9	4	<18: 0.03 18: 0.04	Fasting plasma TG (primary), HbA1c (primary)

†Mean±SD AGL – Acquired generalised lipodystrophy; CGL – Congenital generalised Lipodystrophy; FPLD – Familial partial lipodystrophy; SD – Standard deviation; TG – Triglycerides; yrs - Years

Table 78: Metreleptin Study Results: NIH20010796

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Javor *et al.* 2005(32) *Full Article*	Prospective Open-label, Single arm	GL 87% Female Age (yrs) :23±3	15	12	Female: 0.06–0.08 Male: 0.04	TG, HbA1c (primary), Serum leptin

Park *et al*. 2007(70) *Full Article*	Prospective open-label, Single arm	FPLD 100% Female Age (yrs):33-64	6	12	0.08	TG (primary), HbA1c (primary), Serum leptin

†Mean±SD

BMI - Body mass index; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; PL – Partial lipodystrophy; SD – Standard deviation; TC – Total Cholesterol; TG – Triglycerides; yrs - Years

Table 79: Metreleptin Study Results: RO1 DK88114

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Meral *et al.* 2018(162) *Abstract*	Open-label cohort	PL 78.3% Female	23	12		TG, HbA1c, Leptin

†Mean±SD

PL – Partial lipodystrophy; SD – Standard deviation; TG - Triglycerides

Table 80: Metreleptin Study Results: Others

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Ajluni *et al.* 2017c(163) *Abstract*	Open-label	PL	23	12		TG, Leptin
Akinci *et al.* 2017c(47) *Abstract*	Retrospective cohort	GL, PL (Treated, Naïve)	Treated:178 Naïve: 112			ALT, AST
Amarnath *et al*. 2011(164) *Abstract*	Prospective open-label, Single arm	PL	14	9–18	0.04–0.12	TG (primary), HbA1c (primary)
Araujo-Vilar *et al.* 2015(59) *Abstract*	Retrospective	LD	9	9-60	0.05-0.24	TG, HbA1c (primary), Leptin

Asthana *et al.* 2015(165) *Abstract*	Prospective open-label, Single arm	GL, PL	17	4-8		TG (primary), Serum leptin
Beltrand *et al.* 2007(166)(166) *Full Article*	Prospective open-label, Single arm	Children with BSCL Age (yrs): 2.4-13.6	7	4	Month 1: 0.015 Month 2: 0.03 Month 3 & 4: 0.06	TG (primary), Leptin
Beltrand *et al.* 2010(167) *Full Article*	Prospective open-label, Single arm	Children with BSCL Age(yrs): 5.12-15.81	8	28	0.06-0.12	TG (primary), HbA1c, Leptin, AST, ALT
Ceccarini *et al.* 2018(168)2018(168) *Abstract*	Retrospective cohort	PL, GL	6	3±25		TG (primary), HbA1c (primary)
Cook *et al.* 2018a(169) *Abstract*	Retrospective cohort	AGL, CGL Age (yrs): 3.7	21	61±52		TG (primary), HbA1c (primary)
Cook *et al.* 2018b(170) *Poster*	Retrospective, Single arm	AGL, CGL 54% Female Age (yrs): 17.4±14.9†	28	68±49	Baseline: 3.2 mg/d Month 12: 3.8 mg/d	Fasting TG (primary), HbA1c (primary)
Ebihara *et al.* 2007(171) *Full Article*	Prospective follow-up	AGL, CGL Age (yrs): 21±3†	7	36		TG (primary), HbA1c, Leptin
Joseph *et al.* 2013(172) *Abstract*	Prospective open-label	AGL, APLD, CGL, FPLD 86% Female	68	Point of lowest TG: 18		TG, HDL (primary)
Lightbourne *et al.* 2017(173) *Abstract*	Prospective	LD	14	6	2 weeks: 5mg twice daily 6 months: 4.5 ±1.0mg† twice daily	TG, HDL
Lima *et al.* 2017a(174) *Abstract*	Non-blinded Single arm	CGL 46% Female	11	3	0.46±0.28ml/day†	TG, HbA1c, ALT , AST

Lima *et al.* 2017b(175) *Poster*	Non-blinded Single arm	CGL 46% Female	11	3	0.46± 0.28ml/day†	TG, HbA1c, ALT, AST
Lungu *et al.* 2012(176) *Full Article*	Prospective open-label	AGL, APL, CGL, CPL 100% Female	23	12	0.06-0.24	TG, HbA1c, Leptin
McDuffie *et al.* 2004(177) *Full Article*	Open-label Single arm	AGL, CGL, FPLD 100% Female Age (yrs): 25.4±12.5†	8	4	0.03–0.04	TG, HbA1c, Leptin, Satiation (primary), Satiety (primary), Intake (primary)
Schlögl *et al.* 2016(178) *Full Article*	Prospective open-label, Single arm	GL, PL 78% Female Age (yrs): 16-55	9	12	Female: 5mg/d Male:2.5 mg/d	TG, HbA1c, Leptin, Satiety (primary), Fasting Hunger (primary)
Vatier *et al.* 2016(179) *Abstract*	Prospective	FPLD, CGL 88% Female Age (yrs): 39.2±4†	16	12		TG, HbA1c
Zadeh *et al.* 2012(180) *Abstract*	Prospective open-label	AGL, APL, CGL, FPLD 84% Female	50			TG, HbA1c, ALT (NASH) (primary)

†Mean±SD *Assuming 30 days in a month

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; APL – Acquired partial lipodystrophy; BMI – Body mass index; BSCL – Berardinelli-seip congenital lipodystrophy; CGL – Congenital generalised Lipodystrophy; CPL – Congenital Partial Lipodystrophy; FPLD – Familial partial lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; SD – Standard deviation; Yrs – years

Other studies (non-metreleptin)

The results of the SLR of publications which did not include a metreleptin intervention, grouped by region, are presented in tables Table 81-Table 84.

Table 81: Non-Metreleptin Study Results: USA

Primary Study Reference	Study Design	Population	N	Concomitant Medications	Outcomes of Interest
Ahmad *et al.* 2013(181) *Full Text*	RCT, Double Blind Placebo-Controlled Crossover	APL, GPL	18	Cholic Acid (intervention), Statins, Fibrates, Fish Oil, Metformin, Insulin, Sulfonylurea, Thiazolidinediones	TG, HbA1c, ALT, AST
Ajluni *et al.* 2017a(182) *Full Article*	Cross-sectional, Observational	APL, FPLD	23	Insulin, Metformin, Statins, Fibrate, Fish Oil	Fasting TG, HbA1c, Leptin, ALT, AST
Akinci *et al.* 2018b(183) *Abstract*	Longitudinal, Observational, Multi-Centre Medical Chart Review	AGL, CGL, GL 58.9% Female	56		
Akinci *et al.* 2018c(45) *Poster*	Longitudinal, Observational, Multi-Centre Medical Chart Review	AGL, CGL, GL Age (yrs):11.5	56		TG
Akinci *et al.* 2019(15) *Full Article*	Retrospective, Observational, Natural History Study	Non-HIV GL and PL Age (yrs): 26.2	230		TG, HbA1c, ALT, AST
Haque *et al*. 2003(42) *Full Article*	Cross-sectional, Observational	FPLD 67% Female	76	Lipid-lowering medications, Insulin	TG, HbA1c, Leptin
Joy *et al.* 2008(184) *Full Article*	Retrospective, Observational	FPLD 100% Female Age (yrs): 18-80	25		TG
Oral *et al.* 2015a(185) *Abstract*	Retrospective Cohort, Observational	GL, PL	1637		TG

Oral *et al.* 2015b(186) *Abstract*	Retrospective Cohort, Observational	APLD, CGL, FPLD, Localised LD	1606		TG

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; APL – Acquired partial lipodystrophy; BMI – Body mass index; BSCL – Berardinelli-seip congenital lipodystrophy; CGL – Congenital generalised lipodystrophy; FPLD – Familial partial lipodystrophy; GL – Generalised lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; TC – Total cholesterol; TG – Triglycerides.

Table 82: Non-Metreleptin Study Results: Brazil

Primary Study Reference	Study Design	Population	N	Concomitant Medications	Outcomes of Interest
Akinci *et al.* 2019(15) *Full Article*	Retrospective, Observational, Natural History Study	Non-HIV GL and PL Age (yrs): 26.2±18.4†	230		TG, HbA1c, ALT, AST
Do Rêgo *et al.* 2010(187) *Full Article*	Cross-sectional, Observational	BSS 63.7% Female	22		TG
Foss-Freitas *et al.* 2011(188) *Abstract*	Cross-sectional, Observational	FLPD 100% Female	13		TG, HbA1c
Lima *et al.* 2016(48) *Full Article*	Cross-sectional, Observational	BSCL 62% Female Age (yrs): 21.3±13.7†	54	Insulin, Fibrates	TG, HbA1c, Leptin, ALT, AST
Lima *et al*. 2018(189) *Full Article*	Retrospective, Observational	BSCL 60% Female Age (yrs): 27.1±12.4†	20		

Montenegro *et al*. 2017(190) *Abstract*	Retrospective, Observational	CGL 62% Female Age (yrs): 7.8±10.6 †	21		TG, HbA1c, Serum leptin, ALT, AST
Ponte *et al*. 2018(191) *Full Article*	Retrospective, Cross-sectional, Observational	CGL 58% Female	CGL:10 DM1: 20 Controls:20	Insulin, Metformin	TG, HbA1c, Leptin
Ponte *et al.* 2019(192) *Full Article*	Cross-sectional, Observational	CGL	CGL:10 Controls:20	Insulin, Metformin	
Guedes Do Rego *et al.* 2009(193) *Abstract*	Cross-sectional, Observational	CGL	22		TG, HDL
Godoy-Matos *et al*. 2015(194) *Full Article*	Cross-sectional, Observational	FPLD 100% Female	FPLD:6 Controls:6		TG

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; APL – Acquired partial lipodystrophy; BMI – Body mass index; BSCL – Berardinelli-seip congenital lipodystrophy; CGL – Congenital generalised lipodystrophy; FPLD – Familial partial lipodystrophy; GL – Generalised lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; TC – Total cholesterol; TG – Triglycerides.

Table 83: Non-Metreleptin Study Results: Turkey

Primary Study Reference	Study Design	Population	N	Concomitant Medications	Outcomes of Interest
Akinci *et al.* 2015(195) *Full Text*	Prospective, Follow up, Observational	APL Age (yrs): 30 (median)	21	C-peptide/insulin, Metformin, Fenofibrate	TG, HbA1c
Akinci *et al.* 2016(196) *Full Text*	Retrospective Review & Prospective Follow Up Natural History Study, Observational	CGL	CGL:33 Controls:30	Insulin, Metformin, Fenofibrate, Fish Oil, Medical Nutrition Therapy	TG, HbA1c, Leptin, ALT, AST,

Akinci *et al.* 2017a(197) *Full Text*	Prospective, Multi-centre, Observational	FPLD	FPLD:53 Controls:30	Insulin, Metformin, Statins, Fibrate, Fish Oil	TG, Leptin, ALT,
Akinci *et al.* 2017b(198) *Full Text*	Retrospective Review & Prospective Follow Up, Observational	APL, CGL, FLPD	LD:74 Controls:20	Glucose lowering treatments, Insulin	TG, HbA1c, Leptin, ALT,
Akinci *et al*. 2018a(199) *Full Text*	Prospective Follow Up Multi-Centre, Observational	GL, FLPD 74% Female	81		TG, HbA1c, ALT, Fasting Leptin
Akinci *et al.* 2018b(183) *Abstract*	Longitudinal, Observational Multi-Centre Medical Chart Review	AGL, CGL, GL 58.9% Female	56		
Akinci *et al.* 2018c(45) *Poster*	Longitudinal, Observational, Multi-Centre Medical Chart Review	AGL, CGL, GL Age (yrs): 11.5	56		
Akinci *et al.* 2019(15) *Full Article*	Retrospective, Observational, Natural History Study	Non-HIV GL & PL Age (yrs): 26.2±18.4†	230		TG, HbA1c, ALT, AST
Ozgen Saydam *et al.* 2019(200) *Full Article*	Retrospective, Observational	APL	APL (severe metabolic abnormalities) :6 APL:22	Insulin, Oral Antidiabetics, Metformin, Fenofibrate, Fish Oil	TG, HbA1c, Leptin, ALT

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; APL – Acquired partial lipodystrophy; BMI – Body mass index; BSCL – Berardinelli-seip congenital lipodystrophy; CGL – Congenital generalised lipodystrophy; FPLD – Familial partial lipodystrophy; GL – Generalised lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; TC – Total cholesterol; TG – Triglycerides.

Table 84: Non-Metreleptin Study Results: Other/Not Reported

Primary Study Reference	Study Design	Population	N	Concomitant Medications	Outcomes of Interest

Araujo *et al.* 2015(201) *Abstract*	Retrospective, Observational	BSS	7	Diet Therapy	
Bidault *et al.* 2013(202) *Full Article*	Retrospective, Observational	FPLD 84% Female Age (yrs): 49.5±2.8†	19		TG, HbA1c
Dos Santos *et al.* 2018(203) *Abstract*	Prospective, Observational	PL, FPLD Age (yrs): 18–65	PL:7 FPLD:8 Controls:15		
Fernandes *et al.* 2018[72] *Abstract*	Cross-sectional, Observational	CGL	CGL:10 Controls:20		TG
Guillín-Amarelle *et al.* 2016(204) *Full Article*	Case-controlled, Observational	FPLD 100% Female	FPLD1:98 FPLD2:25 Controls:60		Plasma TG, HbA1c, Plasma leptin, ALT, AST
Hsu *et al.* 2019(205) *Full Article*	Retrospective, Observational	CGL 50% Female Age (yrs): 0.333	16	Fenofibrate, Fat-restricted Diet, combination therapy, Oral hypoglycaemic agents, Insulin	TG, Leptin, ALT, AST
Oral *et al.* 2015c(206) *Abstract*	Retrospective, Observational	FPLD 92% Female Age (yrs): 44, 9-69	59		Hunger/Satiety Measures
Papendieck *et al.* 2018(207) *Full Text*	Retrospective	CGL 75% Female Age (years):1.1 (median)	8	Dietary Therapy (intervention)	TG, ALT, AST
Parente *et al.* 2018(208) *Abstract*	Retrospective Descriptive	BSCL	4	Insulin (intervention)	TG, HbA1c, Leptin

Ponte *et al.* 2016(209) *Abstract*	Cross-sectional, Observational	CGL	CG:10 DM1:20 Controls:20		HbA1c
Sorkina *et al*. 2016(210) *Abstract*	Observational, Clinical	GL, PL 75% Female Age(yrs): 33.8, 2-78	52		HbA1c

†Mean±SD

AGL – Acquired generalised lipodystrophy; ALT – Alanine transaminase; AST – Aspartate transaminase; APL – Acquired partial lipodystrophy; BMI – Body mass index; BSCL – Berardinelli-seip congenital lipodystrophy; CGL – Congenital generalised lipodystrophy; FPLD – Familial partial lipodystrophy; GL – Generalised lipodystrophy; HDL – High density lipoprotein; LDL – Low density lipoprotein; LMNA – Lamin A/C; NASH – Non-alcoholic steatohepatitis; PL – Partial lipodystrophy; PPARG – Peroxisome proliferator activated receptor gamma; TC – Total cholesterol; TG – Triglycerides.

17.6.2 Unpublished Studies

Table 85: Unpublished Study Results

Primary study reference (Full or abstract)	**Study design**	**Population**	**Number of Patients**	**Treatment duration** (months)	**Treatment dose** (mg/kg/d)	**Outcomes of interest** (Primary - primary endpoint)
Tuttle *et al.* (2018) *Full Text*	Extended follow-up	GL, PL 83% Female	112	12		TG, HbA1c, Leptin, ALT, AST

†Mean±SD

PL – Partial lipodystrophy; SD – Standard deviation; TG - Triglycerides

17.7 Appendix 7: Addenbrooke's Hospital early-access program data: Organ Damage and Complications at Baseline

Table 86: Organ Damages and Complications at Baseline from Addenbrooke's Hospital early-access program data

Organ Damage and Complications, n (%)	GL (N=9)	PL (N=11)[a]	Total (N=20)
Any Organ Damage[b]	9 (100)	11 (100)	20 (100)
Liver Damage[c]	9 (100)	11 (100)	20 (100)
Cirrhosis	1 (11)	0 (0)	1 (5)
Hepatic steatosis	5 (56)	11 (100)	16 (80)
Hepatomegaly	4 (44)	2 (18)	6 (30)
Mild to severe fibrosis	1 (11)	0 (0)	1 (5)
Other[d]	3 (33)	0 (0)	3 (15)
Heart Damage[e]	3 (33)	2 (18)	5 (25)
Atherosclerosis	0 (0)	2 (18)	2 (10)
Left ventricular hypertrophy	2 (22)	0 (0)	2 (10)
Other[f]	1 (11)	0 (0)	1 (5)
Kidney Damage[g]	4 (44)	1 (9)	5 (25)
Kidney failure (requiring dialysis or transplant)	1 (11)	0 (0)	1 (5)
Macroalbuminuria	1 (11)	0 (0)	1 (5)
Microalbuminuria	2 (22)	0 (0)	2 (10)
Nephropathy	1 (11)	1 (9)	2 (10)
Other[h]	2 (22)	1 (9)	3 (15)
Pancreatitis	2 (22)	1 (9)	3 (15)
Other Complications [9]			
Diabetes	9 (100)	10 (91)	19 (95)
Retinopathy	1 (11)	3 (27)	4 (20)
Neuropathy	1 (11)	2 (18)	3 (15)
Nephropathy	1 (11)	1 (9)	2 (10)
Other diabetes complications	1 (11)	0 (0)	1 (5)
Depression	1 (11)	0 (0)	1 (5)
Mental retardation	2 (22)	0 (0)	2 (10)
Polyphagia and Hyperphagia	2 (22)	0 (0)	2 (10)
Pain/myopathy	1 (11)	1 (9)	2 (10)

Abbreviations: GL, generalised lipodystrophy; PL, partial lipodystrophy

Notes:

[a] One patient with a lipodystrophy genotype/subtype listed as PCYT1A was assigned a lipodystrophy subtype of Familial Partial.

[b] Organ damage metreleptin initiation includes organ damage conditions reported at the baseline visit or up to 2 years prior to baseline.
[c] Other pre-specified liver damage included chronic hepatitis, liver failure, and transplant; there were no reports of these types of damage.
[d] Other (non-pre-specified) liver damage conditions as reported by the clinician included fatty infiltration.
[e] Other pre-specified heart damage included angina, atrial fibrillation, cardiac arrhythmia, cardiomyopathy, heart failure, ischemia, myocardial infarction, and transplant; there were no reports of these types of damage.
[f] Other (non-pre-specified) heart damage conditions as reported by the clinician included enlargement of left atrium with mild tricuspid regurgitation.
[g] Other pre-specified kidney damage included creatinine clearance < 60 mL/min, and transplant; there were no reports of these types of damage.
[h] Other (non-pre-specified) kidney damage conditions as reported by the clinician included enlarged kidneys with increased cortical echogenicity and hepatomegaly, enlarged kidneys with uncertain etiology, and right kidney atrophy with kidney stones.
[i] Other pre-specified complications included amputation, presence of bone cysts, and sleep apnea; there were no reports of these complications.

17.8 Appendix 8: Critical appraisals of study NIH studies 991265/20010769 and FHA101 using the Downs and Black checklist

Table 87: Critical appraisal of study NIH studies 991265/20010769

Study NIH 991265/20010769			
Question		**Yes/ Partially/ No / Unable to determine**	**Score**
Reporting	**Is the hypothesis/aim/objective of the study clearly described?**	Yes, see Section 9.4	1
	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes, see Section 9.4	1
	Are the characteristics of the patients included in the study clearly described?	Yes, see Section 9.4	1
	Are the interventions of interest clearly described?	Yes, see Section 9.4	1
	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes, see Section 9.4	2
	Are the main findings of the study clearly described?	Yes, see Section 9.6	1
	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes, see Section 9.6	1
	Have all important adverse events that may be a consequence of the intervention been reported?	Yes, see Section 9.7	1
	Have the characteristics of patients lost to follow-up been described?	Yes, see Section 9.4	1

	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes, see Section 9.6	1
External validity	**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?**	Unable to determine	0
	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine	0
	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine	0
Internal validity - bias	**Was an attempt made to blind study subjects to the intervention they have received?**	No, this was an open-label trial	0
	Was an attempt made to blind those measuring the main outcomes of the intervention?	Unable to determine	0
	If any of the results of the study were based on "data dredging", was this made clear?	Yes, see Section 9.6	1
	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes, see Section 9.6	1
	Were the statistical tests used to assess the main outcomes appropriate?	Yes, see Section 9.6	1
	Was compliance with the intervention/s reliable?	No, some non-compliance was observed.	0

	Were the main outcome measures used accurate (valid and reliable)?	No, this was a non-randomised study	0
Internal validity - confounding (selection bias)	**Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?**	Yes, see Section 9.4	1
	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes, see Section 9.4	1
	Were study subjects randomised to intervention groups?	No, this was a single arm trial	0
	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No, this was a single arm trial	0
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No, this was a single arm trial	0
	Were losses of patients to follow-up taken into account?	Yes, see Section 9.4	1
Power	**Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?**	No, this was a single arm trial	0
Total			**17**

Source: Study NIH 991265/20010769 CSR (17) Downs and Black, 1998, (88)

Table 88: Critical appraisal of study FHA101

Study FHA101			
Question		**Yes/ Partially/ No / Unable to determine**	**Score**
Reporting	**Is the hypothesis/aim/objective of the study clearly described?**	Yes, see Section 9.4	1
	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes, see Section 9.4	1
	Are the characteristics of the patients included in the study clearly described?	Yes, see Section 9.4	1
	Are the interventions of interest clearly described?	Yes, see Section 9.4	1
	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes, see Section 9.4	2
	Are the main findings of the study clearly described?	Yes, see Section 9.6	1
	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes, see Section 9.6	1
	Have all important adverse events that may be a consequence of the intervention been reported?	Yes, see Section 9.7	1
	Have the characteristics of patients lost to follow-up been described?	Yes, see Section 9.4	1

	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes, see Section 9.6	1
External validity	**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?**	Unable to determine	0
	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine	0
	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine	0
Internal validity - bias	**Was an attempt made to blind study subjects to the intervention they have received?**	No, this was an open-label trial	0
	Was an attempt made to blind those measuring the main outcomes of the intervention?	Unable to determine	0
	If any of the results of the study were based on "data dredging", was this made clear?	Yes, see Section 9.6	1
	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes, see Section 9.6	1
	Were the statistical tests used to assess the main outcomes appropriate?	Yes, see Section 9.6	1
	Was compliance with the intervention/s reliable?	No, some non-compliance was observed.	0

	Were the main outcome measures used accurate (valid and reliable)?	No, this was a non-randomised study	0
Internal validity - confounding (selection bias)	**Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?**	No, this was a multicentre study, see Section 9.4	0
	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes, see Section 9.4	1
	Were study subjects randomised to intervention groups?	No, this was a single arm trial	0
	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No, this was a single arm trial	0
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No, this was a single arm trial	0
	Were losses of patients to follow-up taken into account?	Yes, see Section 9.4	1
Power	**Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?**	No, this was a single arm trial	0
Total			**16**

Source: Study FHA101 CSR (66) and Downs and Black, 1998 (88)

17.9 Appendix 9: NIH studies 991265/200110769 – further exploratory analyses

17.9.1 Exploratory analyses

Effect of metreleptin on hyperphagia

One important effect of metreleptin in patients with lipodystrophy 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 lipodystrophy (12 with GL and 2 with PL) significantly decreased food intake at 4 months from 3,170 kcal/day to 1,739 kcal/day (p=0.019) (89).As reported by Moran and colleagues from the NIH, metreleptin treatment of 14 patients with lipodystrophy (12 with GL and 2 with PL) significantly decreased food intake at 4 months from 3,170 kcal/day to 1,739 kcal/day (p=0.019) (89). 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 significantly decreased satiation time, increased satiety time, decreased energy consumed to produce satiation, and decreased the amount of food desired in the postabsorptive state (177).

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 well as 7 (22%) of 32 with GL patients who were receiving oral antidiabetic medications at baseline. Among the 34 patients with GL who were receiving lipid-lowering therapies at baseline, 8 (24%) were able to discontinue these medications. Many of these patients could discontinue use of baseline 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 (17).

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, 4 patients with PL, and 2 in the PL subgroup. Among the 36 patients with GL, 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 (17).

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 (17).

17.9.2 Controlled Concomitant Medication Full Analysis Set (CFAS)

A tabulated summary of the primary efficacy endpoints in the CFAS population is provided in Table 89.

Table 89: Primary Efficacy Endpoints: Change from Baseline to Month 12 in HbA1c and Fasting Triglycerides using LOCF (CFAS Population)

PARAMETER STATISTIC	GENERALISED LIPODYSTROPHY			PARTIAL LIPODYSTROPHY	
	MALES (N=14)	FEMALES (N=40)	OVERALL (N=54)	PL SUBGROUP[a] (N=23)	OVERALL (N=31)
HbA1c (%)					
BL Value, n	8	23	31	12	17
Mean (SD)	8.3 (2.13)	8.6 (2.22)	8.5 (2.17)	8.2 (1.99)	7.5 (2.03)
Median	8.9	8.7	8.7	7.8	7.1
Min, Max	5.0, 10.4	4.9, 13.7	4.9, 13.7	5.7, 13.3	5.3, 13.3
Month 12 Value, n	7	23	30	11	15
Mean (SD)	6.3 (1.17)	6.8 (1.73)	6.6 (1.62)	7.6 (1.90)	7.2 (1.76)
Median	5.7	6.4	6.3	6.9	6.8
Min, Max	5.0, 8.2	4.6, 10.4	4.6, 10.4	6.2, 12.7	5.6, 12.7
Actual Change from BL, n	7	23	30	11	15

Mean (SD)	-2.0 (1.93)	-1.9 (1.82)	-1.9 (1.81)	-0.7 (0.69)	-0.4 (0.82)
[95% CI]	[-3.8, -0.2]	[-2.6, -1.1]	[-2.6, -1.2]	[-1.2, -0.2]	[-0.9, 0.0]
p-value[b]	0.035	<0.001	<0.001	0.008	0.072
Fasting TG (mmol/L)					
BL Value, n	13	33	46	19	23
Mean (SD)	5.2 (6.58)	9.9 (16.56)	8.6 (14.53)	12.6 (20.21)	11.0 (18.63)
Median	2.5	4.2	3.8	5.7	4.7
Min, Max	1.1, 25.3	0.6, 83.8	0.6, 83.8	1.3, 89.4	1.3, 89.4
Month 12 Value	13	32	45	18	22
Mean (SD)	1.9 (0.96)	3.7 (4.15)	3.2 (3.62)	5.4 (5.47)	5.1 (4.96)
Median	1.7	2.4	2.1	3.9	3.9
Min, Max	0.6, 3.5	0.7, 16.3	0.6, 16.3	1.0, 20.6	1.0, 20.6
% Change from BL, n	13	31	44	18	22
Mean (SD)	-29.1 (43.31)	-25.4 (86.96)	-26.5 (76.17)	-34.0 (31.44)	-19.2 (53.06)
[95% CI]	[-55.3, -2.9]	[-57.3, 6.5]	[-49.7, -3.3]	[-49.6, -18.3]	[-42.7, 4.3]
p-value[b]	0.032	0.114	0.026	<0.001	0.104

Abbreviations: BL, Baseline; CI, Confidence interval; FAS, Full Analysis Set; GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; PL, Partial lipodystrophy; SD, Standard deviation; SEM, Standard error of the mean; TG, Triglyceride.

[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

17.10 Appendix 10: FHA101 expanded access study: supportive evidence

A tabulated summary of outcomes from Study FHA101 is provided in Table 90.

Table 90: 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)
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 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, Haemoglobin A1c; 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(66)

Patient exposure

Among the 9 patients included in the GL group in this study, median overall duration of treatment was 21.3 months. 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 (66).

Across the 7 patients in the PL subgroup, median overall duration of treatment with metreleptin was 53.1 months. 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 NIH studies 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 (66)

Adverse events

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. 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 (66).

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. Among the PL patients not included in the PL subgroup, events of severe intensity were reported in 9 (36%) of the 25 patients (66).

Two (5%) of the 41 patients died during study FHA101, including one patient with GL and one with PL (not in the PL subgroup). 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 (66).

Overall, 6 (67%) of the 9 GL patients experienced at least 1 SAE, none of which was assessed as related to study treatment. There were no SAEs reported in patients in the PL subgroup. Ten patients with PL who were not in the PL subgroup experienced SAEs (66).

Discontinuations due to TEAEs were reported in the 2 patients who died and in 2 additional patients with PL (not in the PL subgroup) (66).

A tabulated summary of adverse events in Study FHA101 is provided in Table 91.

Table 91: 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)	5 (15.6)
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)

	GL (N = 9)	PL subgroup[a] (N = 7)	PL overall (N = 32)
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 HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L

Source: Study FHA101 CSR(66)

17.11 Appendix 11: Pooled safety analysis

A pooled safety analysis of metreleptin adverse reactions across NIH studies 991265/20010769 and study FHA101 is shown in Table 92.

Table 92: 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)
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)

MedDRA SOC Preferred term	All GL patients AND patients in the PL subgroup (N = 113) N (%)
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 (17,66)

17.12 Appendix 12: Indirect treatment comparison

17.12.1 Baseline characteristics and appropriateness for covariate use

Baseline variable	**Measured in NIH follow-up study?***	**Measured in the GL/PL Natural History study?***	**Effect on treatment assignment?**	**Effect on outcomes (HbA1c, TG levels, pancreatitis, liver enzymes [AST and ALT] and mortality)?**	**Desired covariate?**
Demographic covariates					
Gender	✓	✓	Yes – treated patients were mostly female but natural	Yes - gender affects mortality at baseline and possibly	Yes

			history patients were mostly male.	underlying disease severity and profile.	
Ethnicity	✓	✓	Yes – more Caucasians on treatment.	No – assumption, validated by clinicians at Addenbrooke's.	No
Country of origin	✓	✓	Yes – more US patients on treatment.	No - assumption	No
Age at first GL/PL symptoms	✓	✓	Yes - this age is lower in the treated patients.	Yes - assumption	No – this a confounding variable with age at baseline. Age at baseline is preferred because there is less ambiguity.
Age at diagnosis	✗	✓	Not applicable	Not applicable	No
Age at baseline	✓	✓	Yes - this age is lower in the treated patients.	Yes - age affects mortality at baseline and possibly underlying disease severity and profile.	Yes
Number and type of physician involved in care	✗	✓	Not applicable	Not applicable	No
Lipodystrophy subtype					
Lipodystrophy type (APL, AGL, CGL, FPLD)	✓	✓	Yes – more treated patients with GL.	Yes – PL patients in general have a better prognosis.	Yes
Generalised progeroid lipodystrophy	✗	✓	Not applicable	Not applicable	No
Subtype within AGL/AGL, CGL, FPLD, progeria.	✗	✓	Not applicable	Not applicable	No
Genetic mutation	✓	✓	Unclear	No or unknown - assumption	No
Physical covariates					

Acanthosis nigricans present	✗	✓	Not applicable	Not applicable	No
Acromegaloid features present	✗	✓	Not applicable	Not applicable	No
Lack of fat in face present	✗	✓	Not applicable	Not applicable	No
Hepatomegaly present	✗	✓	Not applicable	Not applicable	No
Muscular appearance present	✗	✓	Not applicable	Not applicable	No
Prominent veins present	✗	✓	Not applicable	Not applicable	No
Prognathism present	✗	✓	Not applicable	Not applicable	No
Splenomegaly present	✗	✓	Not applicable	Not applicable	No
Laboratory values					
HbA1c levels	✓	✓	Yes – baseline HbA1c was higher in treated patients.	Yes – HbA1c levels in an appropriate range would indicate a better prognosis.	Yes
TG levels	✓	✓	Yes – baseline TG was lower in treated patients.	Yes – TG levels in an appropriate range would indicate a better prognosis.	Yes
LDL levels	✗	✓	Not applicable	Not applicable	No
HDL levels	✗	✓	Not applicable	Not applicable	No
Leptin levels	✓	✓	Yes – baseline leptin was lower in treated patients.	Yes – leptin levels in an appropriate range would indicate a better prognosis.	Yes
ALT levels	✓	✓	Yes – more patients with elevated ALT in the NIH study.	Yes – ALT levels in an appropriate range would indicate a better prognosis.	Yes
AST levels	✓	✓	Yes – more patients with elevated AST in the NIH study.	Yes – AST levels in an appropriate range would indicate a better prognosis.	Yes

GGT levels	✗	✓	Not applicable	Not applicable	No
Liver volume	✗	✓	Not applicable	Not applicable	No
Liver span	✗	✓	Not applicable	Not applicable	No
Haemoglobin levels	✗	✓	Not applicable	Not applicable	No
Haemocrit levels	✗	✓	Not applicable	Not applicable	No
Medication usage					
Any anti-diabetic medication:	✓	✗	Not applicable	Not applicable	No
Any insulin agent	✗	✓	Not applicable	Not applicable	No
Any oral antidiabetic agent	✗	✓	Not applicable	Not applicable	No
Any GLP-1 analogue agent	✗	✓	Not applicable	Not applicable	No
Metformin plus insulin	✓	✗	Not applicable	Not applicable	No
Basal insulin	✓	✗	Not applicable	Not applicable	No
Bolus insulin	✓	✗	Not applicable	Not applicable	No
Metformin	✓	✗	Not applicable	Not applicable	No
Other	✓	✗	Not applicable	Not applicable	No
Any TG lowering medication:	✓	✗	Not applicable	Not applicable	No
Fibrate	✓	✓	Not applicable	Not applicable	No
Niacin	✗	✓	Not applicable	Not applicable	No
Fish oil derivative	✗	✗	Not applicable	Not applicable	No
Statin	✓	✓	Not applicable	Not applicable	No
Fibrate plus statin	✓	✗	Not applicable	Not applicable	No
Other	✗	✓	Not applicable	Not applicable	No
Any lipid lowering medication	✗	✓	Not applicable	Not applicable	No
Any elective cholesterol absorption inhibitor	✗	✓	Not applicable	Not applicable	No

Any anti-hypertensive medication:	✓	✗	Not applicable	Not applicable	No
ACE inhibitor	✓	✗	Not applicable	Not applicable	No
Fibrate plus statin	✓	✗	Not applicable	Not applicable	No
Angiotensin II Receptor Antagonists	✓	✗	Not applicable	Not applicable	No
Vital signs					
Height	✓	✓	No – height is similar between studies.	No – assumption validated by clinicians at Addenbrooke's.	No
Weight	✓	✓	No – weight is similar between studies.	Very minor – assumption validated by clinicians at Addenbrooke's.	No
Pulse rate	✓	✓	Yes – higher in patients on treatment.	Very minor – assumption validated by clinicians at Addenbrooke's.	No
Systolic blood pressure	✓	✓	Yes – higher in patients on treatment.	Very minor – assumption validated by clinicians at Addenbrooke's.	No
Diastolic blood pressure	✓	✓	Yes – higher in patients on treatment.	Very minor – assumption validated by clinicians at Addenbrooke's.	No
Respiratory rate	✗	✓	Not applicable	Not applicable	No
Pulse rate	✗	✓	Not applicable	Not applicable	No
Organ abnormalities and other complications/comorbidities					
Number or type of abnormal organs (liver, kidney and heart)	✓	✓	Yes – organ abnormalities indicate general health and therefore prognosis.	Yes – assumed – this is difficult to summarise.	Yes

Pancreatitis	✓	✓	Yes – pancreatitis is assumed to indicate general health and therefore prognosis.	Yes – assumed – this is difficult to summarise.	Yes
Diabetes	✗	✓	Not applicable	Not applicable	No
Cancer	✗	✓	Not applicable	Not applicable	No
Reproductive abnormalities	✗	✓	Not applicable	Not applicable	No
Gastric abnormalities	✗	✓	Not applicable	Not applicable	No
Infections requiring hospitalisation	✗	✓	Not applicable	Not applicable	No
Psychiatric abnormalities	✗	✓	Not applicable	Not applicable	No
Respiratory abnormalities	✗	✓	Not applicable	Not applicable	No
Other abnormalities	✗	✓	Not applicable	Not applicable	No

17.12.2 Rationale for using IPW over multivariate regression

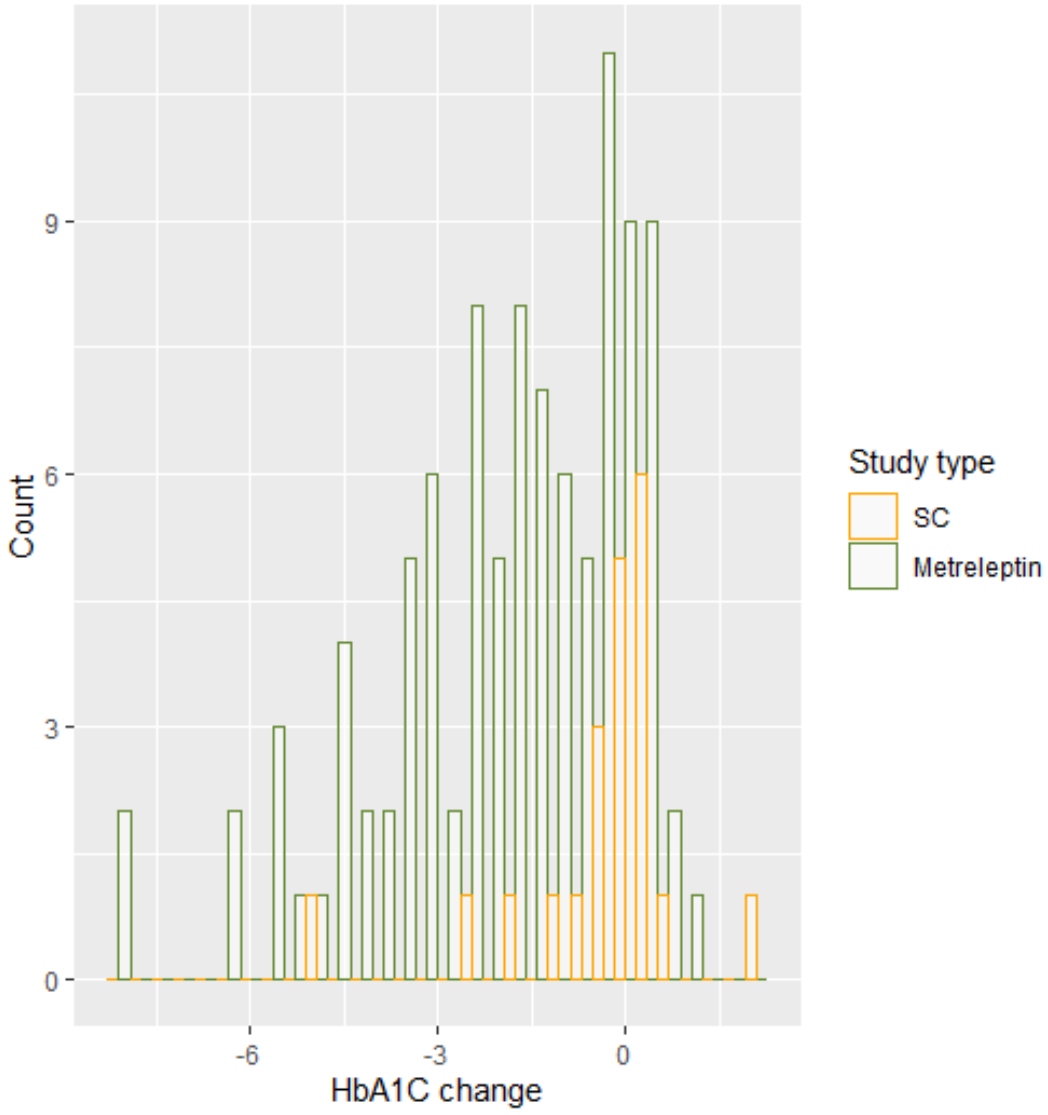
Here we assess the **parametric assumption** of normality for our continuous outcome variables. This is a pre-requisite for regression-based adjustments.

17.12.2.1 HbA1c

A Shapiro-Wilk test suggested violation of normality ($W=0.91$; $p<0.001$). This was supported by a histogram (

Figure 39), which indicated a negative skew of the data.

Figure 39: Histogram illustrating distribution of HbA1c change

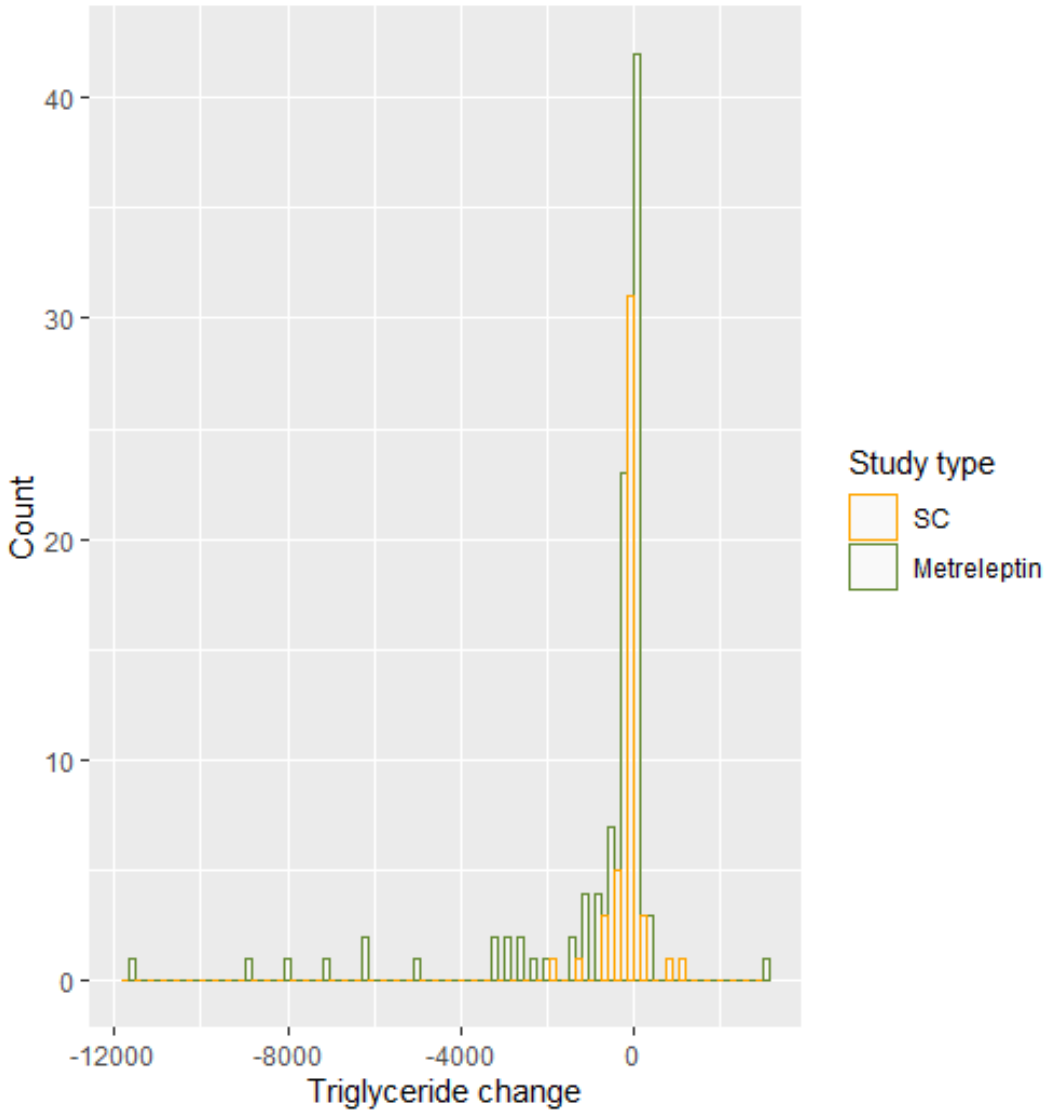


17.12.2.2 Triglycerides

A Shapiro-Wilk test suggested violation of normality (W=0.52; P<0.001). This was supported by a histogram (

Figure 40), which confirmed the skew of the data.

Figure 40: Histogram illustrating distribution of triglyceride change

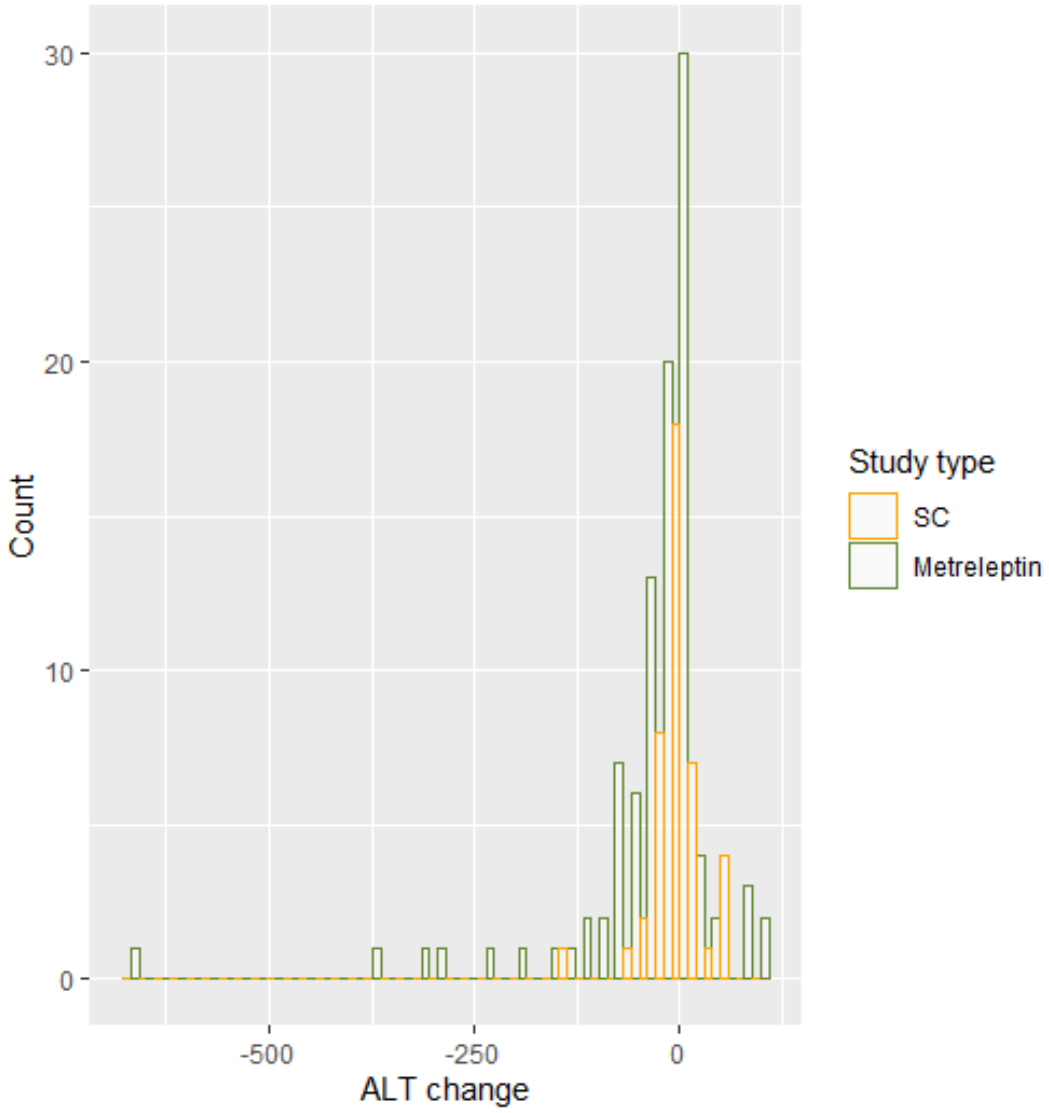


17.12.2.3 ALT

A histogram indicated skewed data (

Figure 41), supported by a Shapiro-Wilk test suggesting a violation of normality (W=0.62; P<0.001), likely due to the small sample size of the GL/PL Natural History study (supportive care).

Figure 41: Histogram illustrating distribution of ALT change

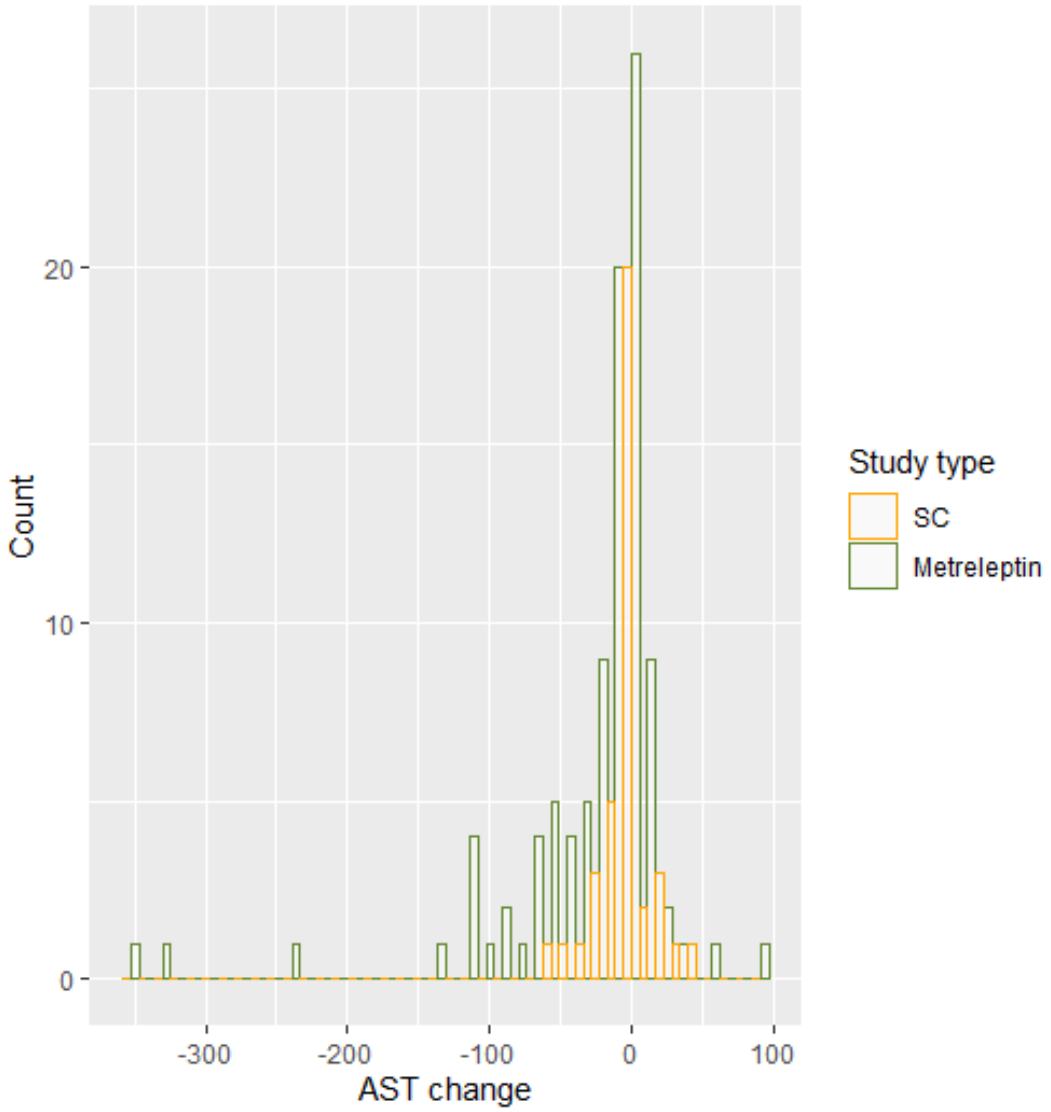


17.12.2.4 AST

A histogram indicated positively skewed data (

Figure 42) confirmed with a Shapiro-Wilk test suggesting a violation of normality (W=0.65; P<0.001), likely due to the small sample size of the GL/PL Natural History study (supportive care).

Figure 42: Histogram illustrating distribution of AST change



The results of these analyses suggest that regression-based adjustments should not be carried out, as the parametric assumption is violated in all continuous variables. We will explore this assumption further in our sensitivity analyses through both the goodness of fit (R^2 for continuous variables and Nagelkerke pseudo R^2 for categorical variables) and Q-Q plots assessing the normality of residuals. Therefore, although we present the results of multivariate regression below as a methodology sensitivity analysis, we will use IPW as our final adjustment method.

17.12.3 Naïve analyses

17.12.3.1 Methodology

A naïve analysis (a benchmark comparison of the NIH follow-up study to the GL/PL Natural History study using unadjusted outcomes) was performed. These consisted of a comparison for the two study populations using a two-

sample t-test (**t.test** function) for continuous outcomes (change in HbA1c, triglyceride levels, ALT and AST at Month 12 compared to baseline); a chi-squared test (**chisq.test** function) for categorical variables (incidence of acute pancreatitis since treatment initiation) and a Cox proportional-hazards model (**survival** package, **coxph** and **survfit** function) using time-to-event data (mortality since treatment initiation). The results of our naïve analyses were illustrated using the **ggplot2** package.

17.12.3.1.1 Mean percentage change in HbA1c

The naïve analysis suggested a significant mean HbA1c reduction at Month 12 from baseline for metreleptin with or without supportive care compared to supportive care ($p<0.001$). A mean change of -1.94% in HbA1c was observed for metreleptin with or without supportive care at Month 12 compared to baseline in the NIH Follow-up study versus supportive care in the GL/PL Natural History study (Table 93,

Figure 43).

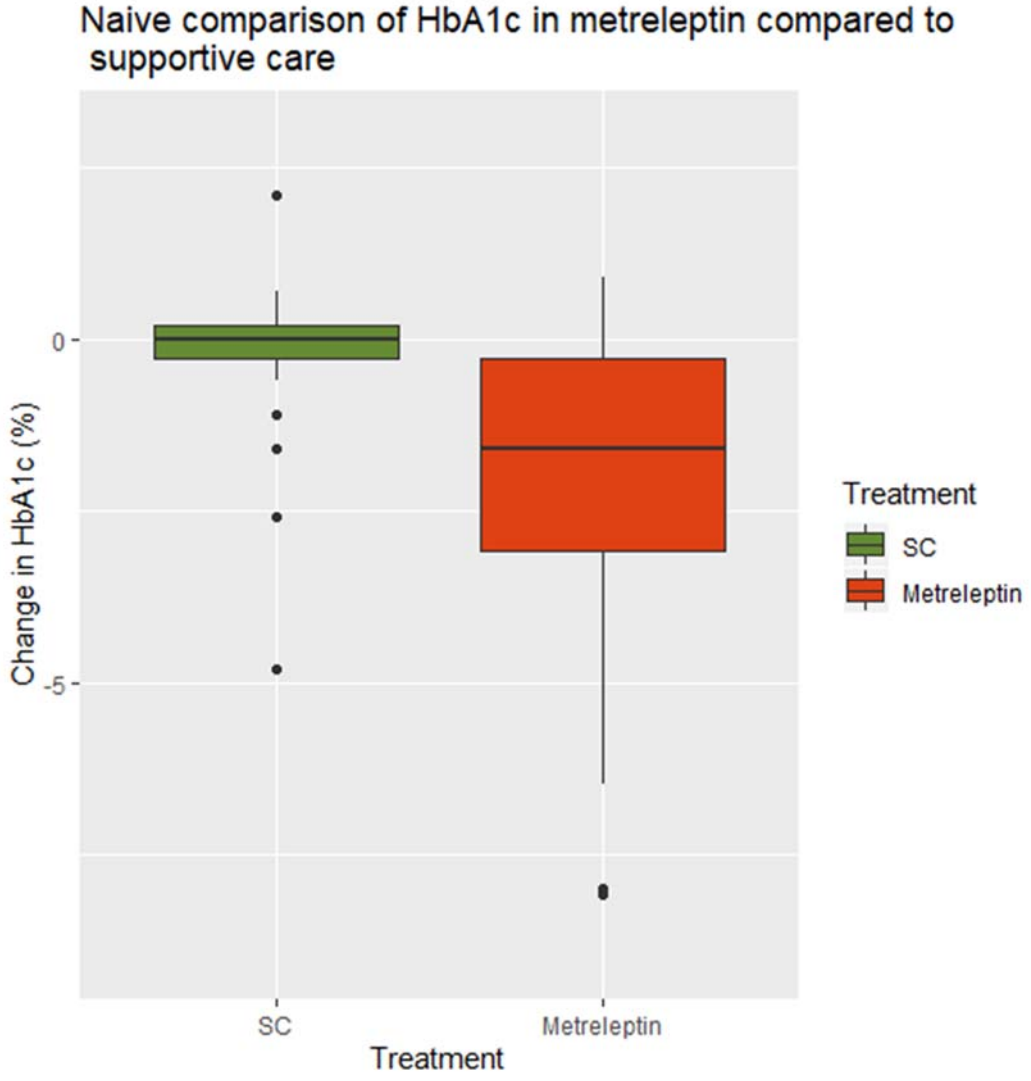
Table 93: Naïve analysis of mean HbA1c change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline

Intervention (study)	Mean HbA1c change (%), at Month 12 from baseline with metreleptin with or without supportive care versus supportive care alone (SD)	95% CI	SE	Absolute HbA1c difference with metreleptin with or without supportive care versus supportive care alone (%)	95% CI, HbA1c difference with metreleptin with or without supportive care versus supportive care alone	p-value
Metreleptin with or without supportive care (NIH Follow-up study)	-1.94 (1.98)	-2.33; -1.55	0.20	1.66	0.90; 2.35	**<0.001***
supportive care (GL/PL Natural History Study)	-0.31(1.38)	-0.94; 0.32	0.30			

Abbreviations: CI, Confidence interval; GL, Generalised lipodystrophy; NIH, National Institutes of Health; PL, Partial lipodystrophy; SD, Standard deviation; SE, Standard error

* denotes significance at the p<0.05 level

Figure 43: Boxplot showing naive comparison of change in HbA1c of metreleptin with or without supportive care compared to standard of care (supportive care) at Month 12 compared to baseline


Naive comparison of HbA1c in metreleptin compared to supportive care
Change in HbA1c (%)
0
-5
SC
Metreleptin
Treatment
Treatment
SC
Metreleptin

17.12.3.1.2 Mean mg/dL change in triglycerides

The naïve analysis suggested a significant mean triglyceride reduction at 1 year from baseline for metreleptin with or without supportive care compared to supportive care alone (p<0.001). A mean change of 932 mg/dL in triglyceride levels was observed for metreleptin from baseline to one year in the NIH Follow-up study compared to the GL/PL Natural History study (Table 94; Figure 44). Results converted from mg/dL to mmol/L are given in square brackets.

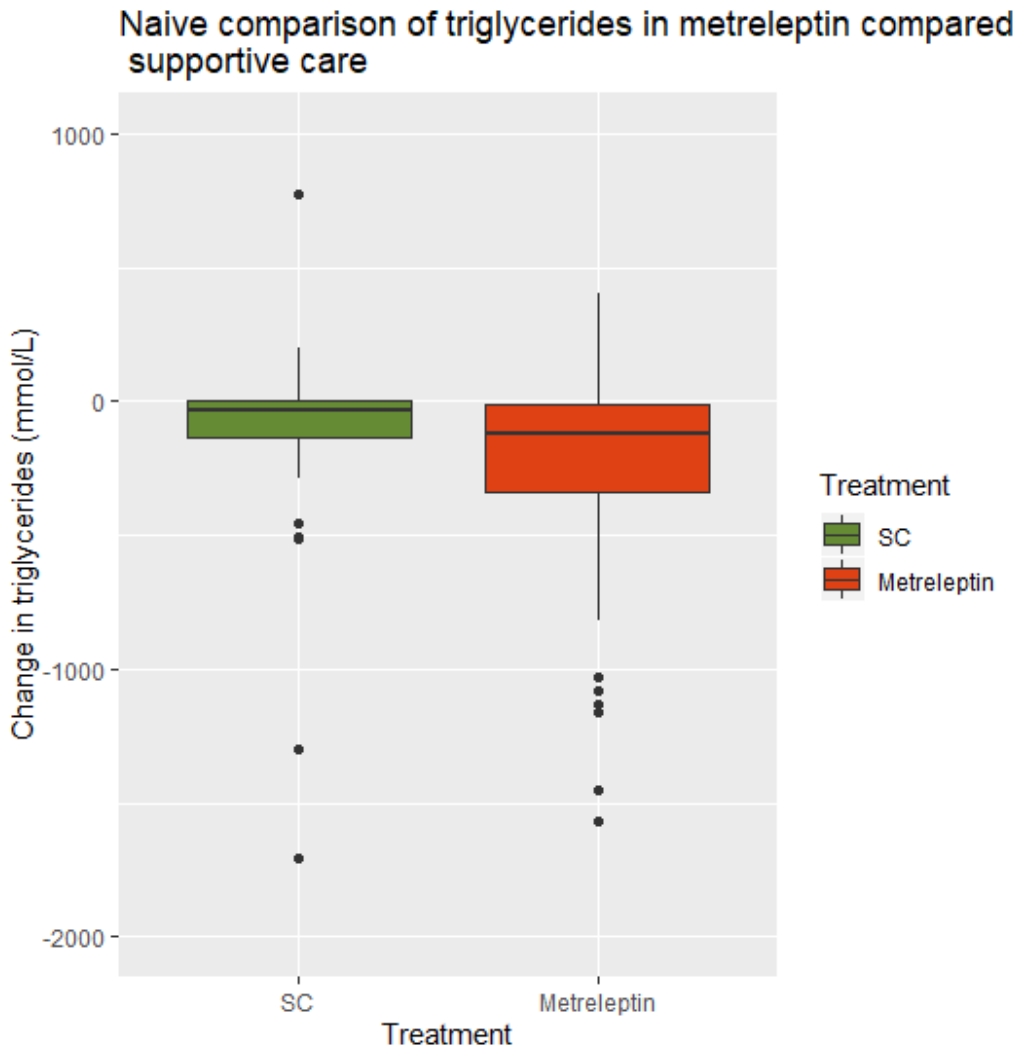
Table 94: Naïve analysis of mean triglyceride change of metreleptin with or without supportive care compared to standard of care (supportive care) at Month 12 compared to baseline

Intervention (study)	**Mean triglyceride change mg/d, [mmol/L] at 1-year from baseline with metreleptin with or without supportive care versus supportive care alone (SD)**	**95% CI** **mg/dl, [mmol/L]**	**SE** **mg/dl, [mmol/L]**	**Absolute triglyceride difference mg/dl, [[mmol/L] with metreleptin with or without supportive care versus supportive care alone**	**95% CI, triglyceride difference with metreleptin with or without supportive care versus supportive care alone, mg/dl [mmol/L]**	**p-value**
Metreleptin with or without supportive care (NIH Follow-up study)	-932.45 (2090.42) [-51.80 (116.13)]	1345.12; -519.77 [74.73; -28.88]	208.00 [11.56]	852.46 [47.36]	423.30; 1281.63 [23.52; 71.20]	**<0.001***
Supportive care (GL/PL Natural History Study)	-79.98 (411.67) [-4.43 (22.87)]	-202.24; 42.27 [-11.24; 2.34]	60.70 [3.38]			

Abbreviations: CI, Confidence interval; GL, Generalised lipodystrophy; NIH, National Institutes of Health; PL, Partial lipodystrophy; SD, Standard deviation; SE, Standard error;

* denotes significance at the p<0.05 level

Figure 44: Boxplot showing naive comparison of change in triglycerides of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline



17.12.3.1.3 Mean U/L change in ALT

The naïve analysis suggested a significant mean ALT reduction of 41.36 from baseline to Month 12 for metreleptin with or without supportive care in the NIH Follow-up study in the compared to supportive care alone ($p<0.001$; Table 95; Figure 45).

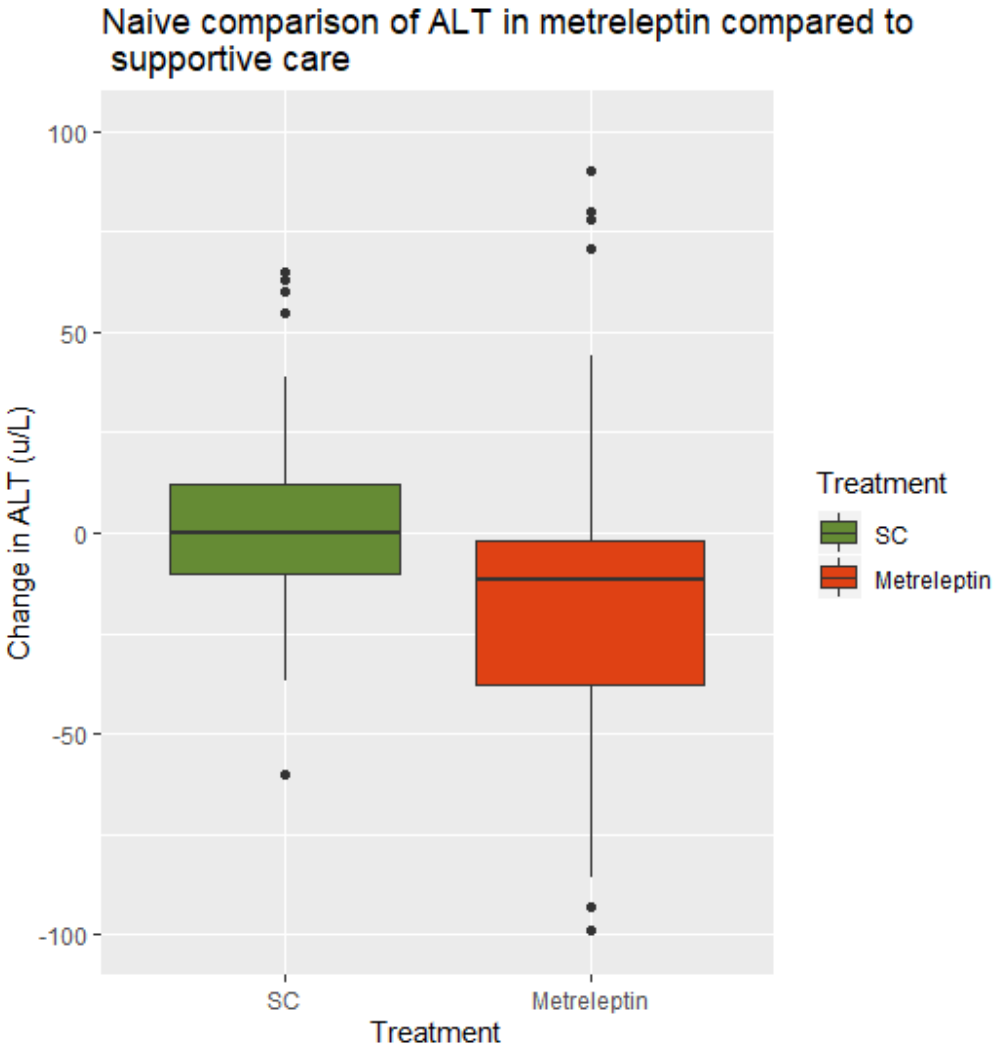
Table 95: Naïve analysis of mean ALT change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline

Intervention (study)	Mean ALT change (U/L), at Month 12 from baseline with metreleptin with or without supportive care versus supportive care alone (SD)	95% CI	SE	Absolute ALT difference (U/L) with metreleptin with or without supportive care versus supportive care alone	95% CI, ALT difference with metreleptin with or without supportive care versus supportive care alone	p-value
Metreleptin with or without supportive care (NIH follow-up study)	-41.36 (96.94)	-60.70; -22.03	9.74	41.07	19.33; 62.81	**<0.001***
Supportive care (GL/PL Natural History Study)	-0.29 (32.97)	-10.57; 9.98	5.09			

Abbreviations: CI, Confidence interval; GL, Generalised lipodystrophy; NIH, National Institutes of Health; PL, Partial lipodystrophy; SD, Standard deviation; SE, Standard error

* denotes significance at the p<0.05 level

Figure 45: Boxplot showing naive comparison of change in ALT of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline



17.12.3.1.4 Mean U/L change in AST

The naïve analysis suggested a significant mean ALT reduction at Month 12 from baseline for metreleptin with or without supportive care compared to supportive care ($p<0.001$). A mean AST change of 26 U/L was observed for metreleptin with or without supportive care at Month 12 compared to baseline in the NIH follow-up study (Table 96; Figure 46).

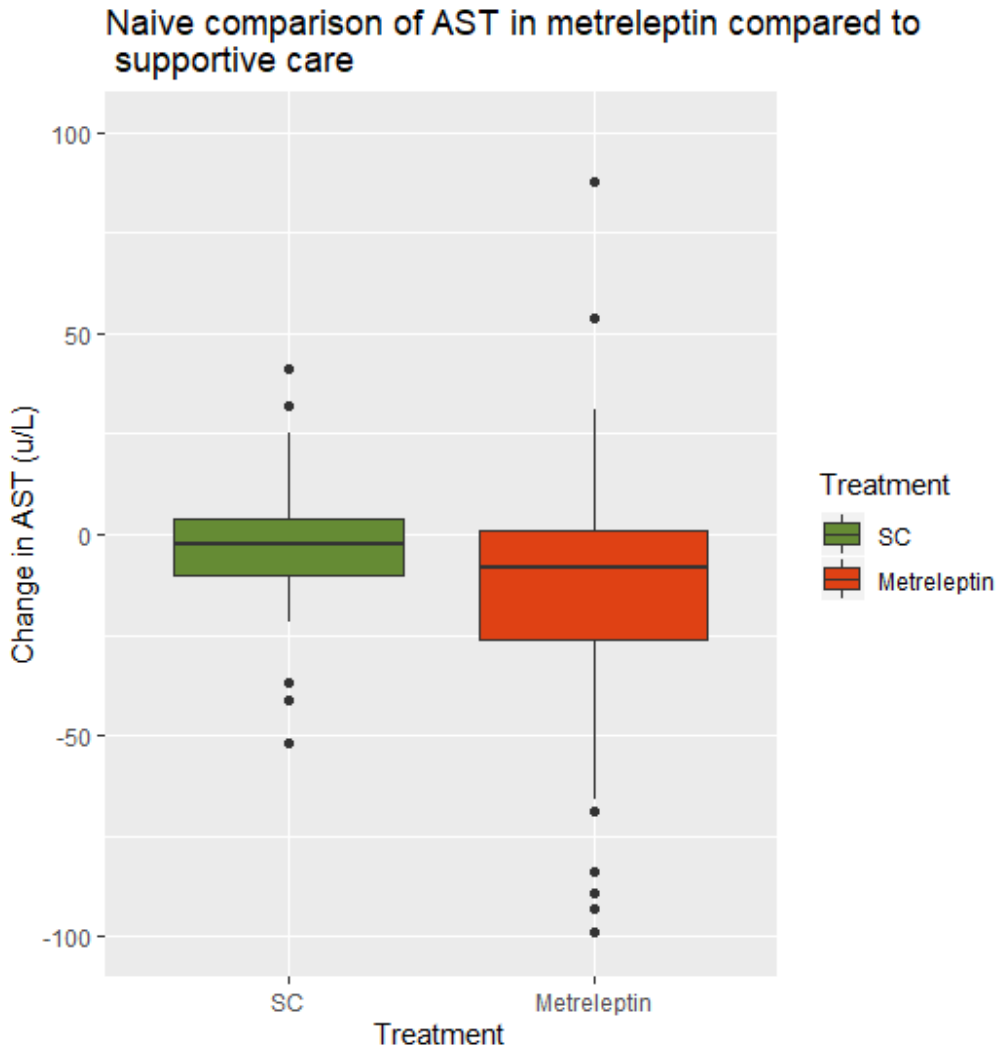
Table 96: Naïve analysis of mean AST change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline

Intervention (study)	**Mean AST change (U/L), at Month 12 from baseline with metreleptin with or without supportive care versus supportive care alone (SD)**	**95% CI**	**SE**	**Absolute AST difference (U/L) with metreleptin with or without supportive care versus supportive care alone**	**95% CI, AST difference with metreleptin with or without supportive care versus supportive care alone**	**p-value**
Metreleptin with or without supportive care (NIH follow-up study)	-29.41 (62.29)	-41.84; -16.99	6.26	26.15	12.50; 39.80	**<0.001***
Supportive care (GL/PL Natural History Study)	-3.27 (17.88)	-9.14; 2.61	2.90			

Abbreviations: CI, Confidence interval; GL, Generalised lipodystrophy; NIH, National Institutes of Health; PL, partial lipodystrophy; SD, Standard deviation; SE, Standard error

* denotes significance at the p<0.05 level

Figure 46: Boxplot showing naive comparison of change in AST of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline



17.12.3.1.5 Incidence of pancreatitis, complete case analysis

The naïve analyses suggested a significant reduction in the number of incidence of pancreatitis between metreleptin with or without supportive care and supportive care alone (p=0.037; Table 97)

Table 97: Naïve analysis of pancreatitis presence post-treatment of metreleptin with or without supportive care compared to supportive care (complete case analysis).

Intervention (study)	No Pancreatitis, n (%)	Pancreatitis, n (%)	p-value
Metreleptin with or without supportive care (NIH Follow-up study)	103 (98.1%)	2 (1.9%)	**0.037***
Supportive care (GL/PL Natural History Study)	176 (91.2%)	17 (8.8%)	

Abbreviations: NIH, National Institutes of Health; GL, Generalised lipodystrophy; PL, Partial lipodystrophy.
* denotes significance at the p<0.05 level

17.12.3.1.6 Incidence of pancreatitis (with imputation)

The naïve analyses suggested a significant reduction in the number of incidence of pancreatitis between metreleptin with or without supportive care versus supportive care alone (p=0.037; Table 98)

Table 98: Naïve analysis of pancreatitis presence post-treatment of metreleptin with or without supportive care compared to supportive care (complete case analysis).

Intervention (study)	No Pancreatitis, n (%)	Pancreatitis, n (%)	p-value
Metreleptin with or without supportive care (NIH Follow-up study)	103 (98.1%)	2 (1.9%)	**0.037***
Supportive care (GL/PL Natural History Study)	176 (91.2%)	17 (8.8%)	

Abbreviations: NIH, National Institutes of Health; GL, Generalised lipodystrophy; PL, Partial lipodystrophy.
* denotes significance at the p<0.05 level

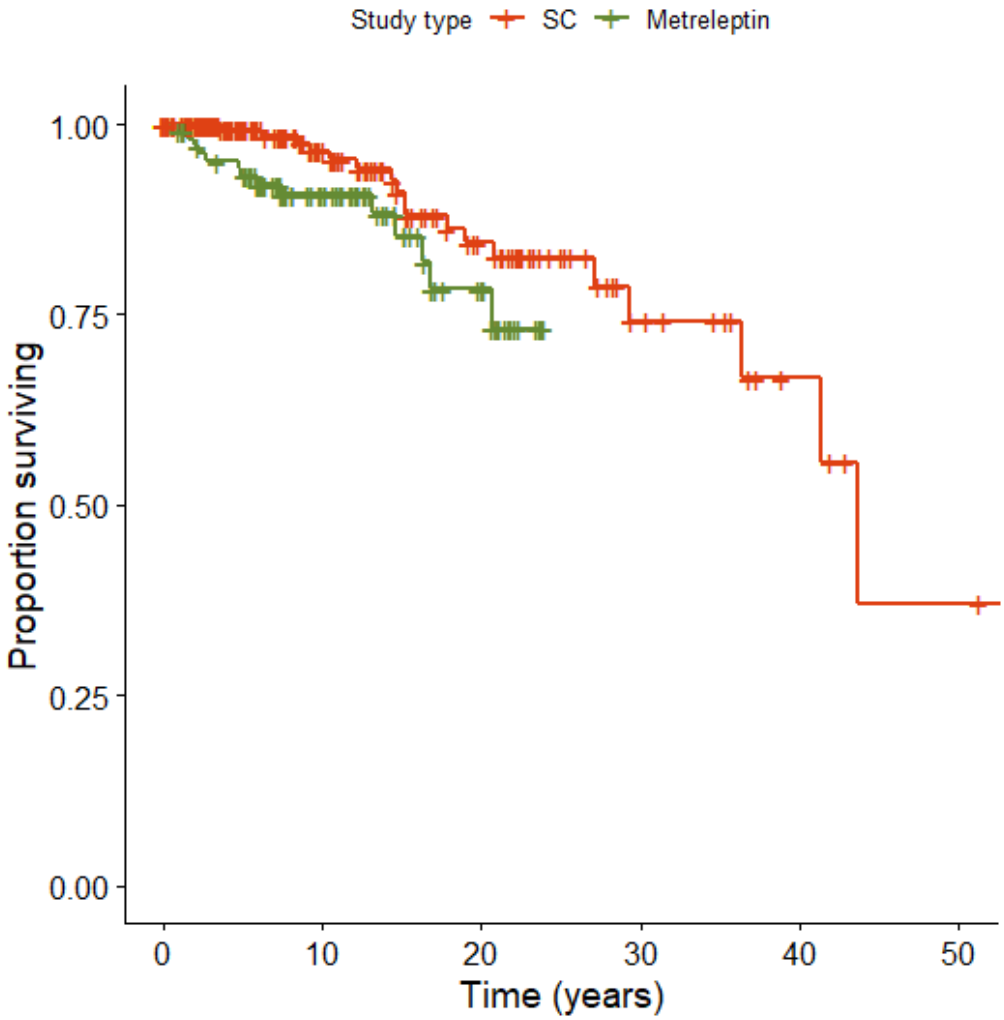
17.12.3.1.7 All-cause mortality

Naïve analyses did not suggest a significant difference in the risk of mortality between metreleptin with or without supportive care and supportive care throughout the duration of the studies (p=0.06065; Table 99; Figure 47).

Table 99: Naïve analysis of mortality post-baseline of metreleptin compared to supportive care

Intervention (study)	N	Number of events	p-value of difference between groups	HR	p-value of HR
Metreleptin with or without supportive care (NIH Follow-up study)	106	14	0.060	2.05	0.065
Supportive care (GL/PL Natural History study)	228	18			
Abbreviations: NIH, National Institutes of Health; HR, Hazard ratio; GL, Generalised lipodystrophy; PL, Partial lipodystrophy					

Figure 47: Naïve Kaplan-Meier curve of metreleptin with or without supportive care and supportive care



17.12.4 Multivariate regression sensitivity analysis

17.12.4.1 Methodology

A simple adjustment methodology involves the assumption that a regression model is a good approximation of the effect of the variables on the outcome. A multivariate regression model is then used, including a dummy variable to represent whether patients were treated with supportive care alone (0) or with metreleptin with or without supportive care (18). This was assessed using the **lm** function for continuous outcomes (change in HbA1c, triglyceride levels, ALT and AST over the course of one year), **glm** function for categorical data (incidence of acute pancreatitis since treatment initiation), and a Cox proportional-hazards model (**survival** package, **coxph** function) for time-to-event outcomes.

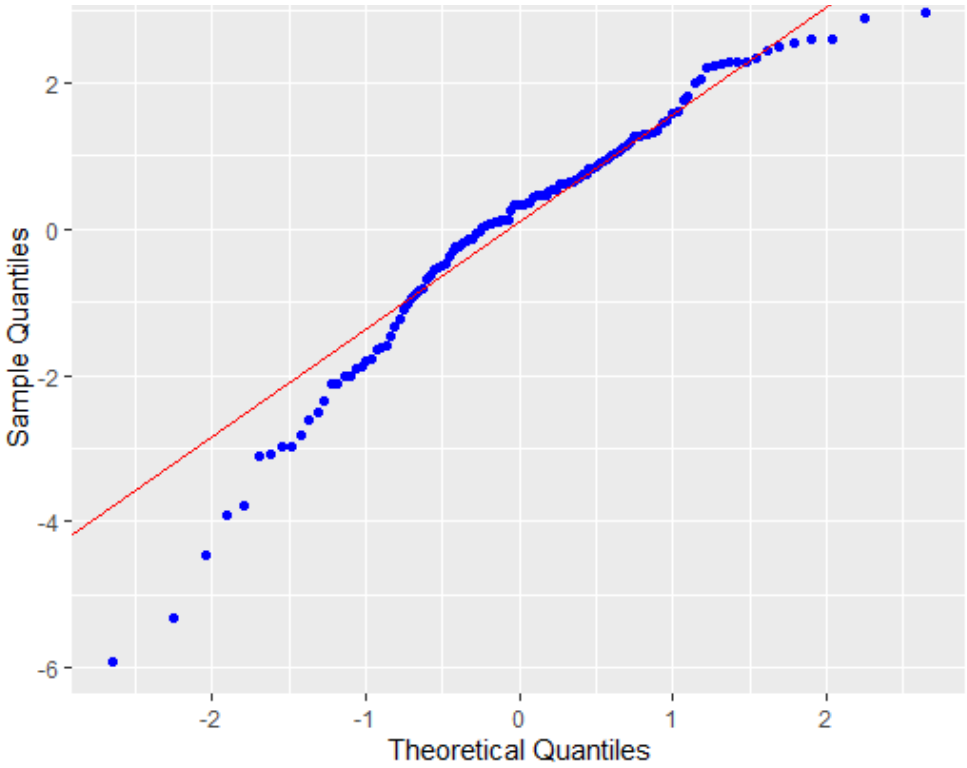
17.12.4.1.1 Mean percentage change in HbA1c

Multivariate analyses show that metreleptin with or without supportive care reduced HbA1c by 0.89% compared to supportive care at Month 12 from baseline. This was not significant (p=0.06; Table 100). A relatively low adjusted R^2 (0.21) alongside a Q-Q plot), (Figure 48) also supported our assumption that a regression model was not a good approximation of the covariates on the outcome of interest).

Table 100: Linear regression of change in HbA1c against study type, age, gender and lipodystrophy type.

	Coefficient (mean HbA1c, %)	**Standard error**	**p-value**	**Adjusted R^2**
ATE of metreleptin with or without supportive care	-0.89	0.47	0.06	0.21
Abbreviations: ATE, Average treatment effect * denotes significance at the p<0.05 level				

Figure 48: Q-Q plot assessing the normality of residuals from HbA1c multivariate regression



17.12.4.1.2 Mean mg/dL change in triglycerides

The multivariate analysis results show that metreleptin with or without supportive care significantly reduce triglyceride levels by 699 mg/dL compared to supportive care at Month 12 from baseline (p=0.039; Table 101). A low adjusted R^2 (0.036), alongside a Q-Q plot (Figure 49) also supported our assumption that a regression model was not a good approximation of the covariates on the outcome of interest. Results converted from mg/dL to mmol/L are given in square brackets.

Figure 49: Q-Q plot assessing the normality of residuals from triglycerides multivariate regression

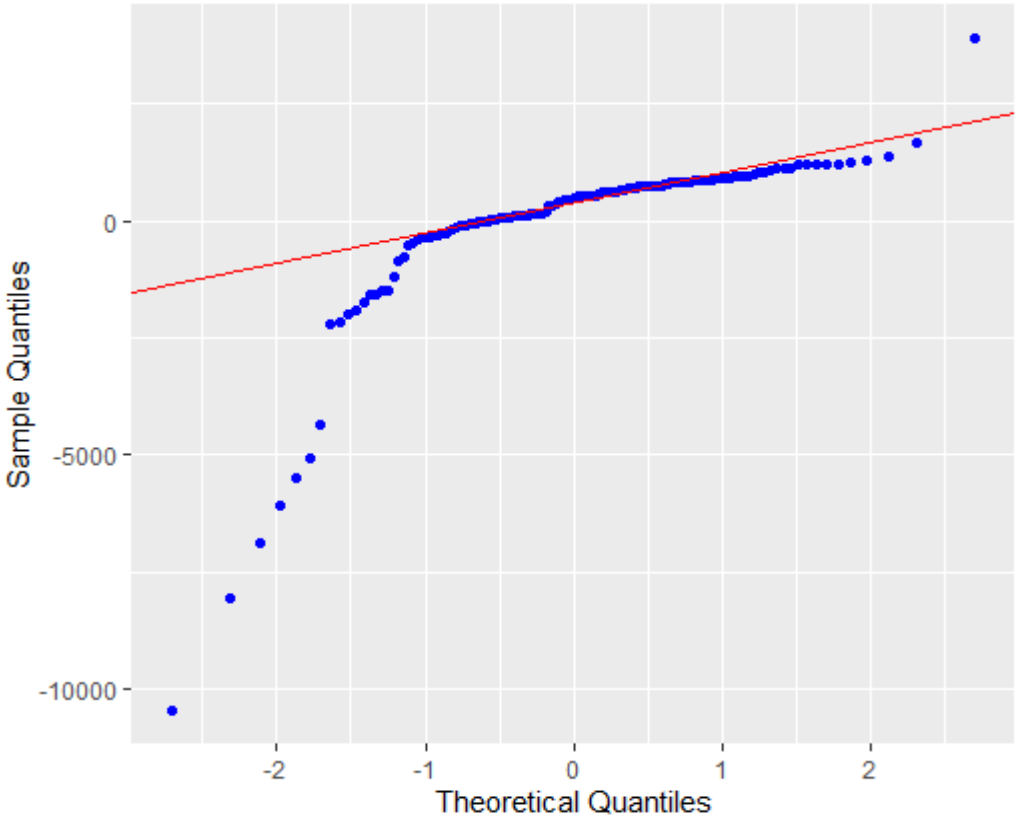


Table 101: Linear regression of change in triglycerides against study type, age, gender and lipodystrophy type.

	Coefficient (triglycerides, mg/dL)	Standard error	p-value	Adjusted R^2

ATE of metreleptin with or without supportive care versus supportive care	-699.07 [-38.84]	335.58 [18.64]	**0.039***	0.036
Abbreviations: ATE, Average treatment effect. * denotes significance at the p<0.05 level				

17.12.4.1.3 Mean U/L change in ALT

The multivariate analysis results showed that metreleptin with or without supportive care significantly reduced AST by 33.4 U/L compared to supportive care at Month 12 from baseline (p=0.035, Table 102). A low adjusted R^2 (0.135), alongside a Q-Q plot (Figure 51), also supported our assumption that a regression model was not a good approximation of the covariates on the outcome of interest.

Figure 50: Q-Q plot assessing the normality of residuals from ALT multivariate regression

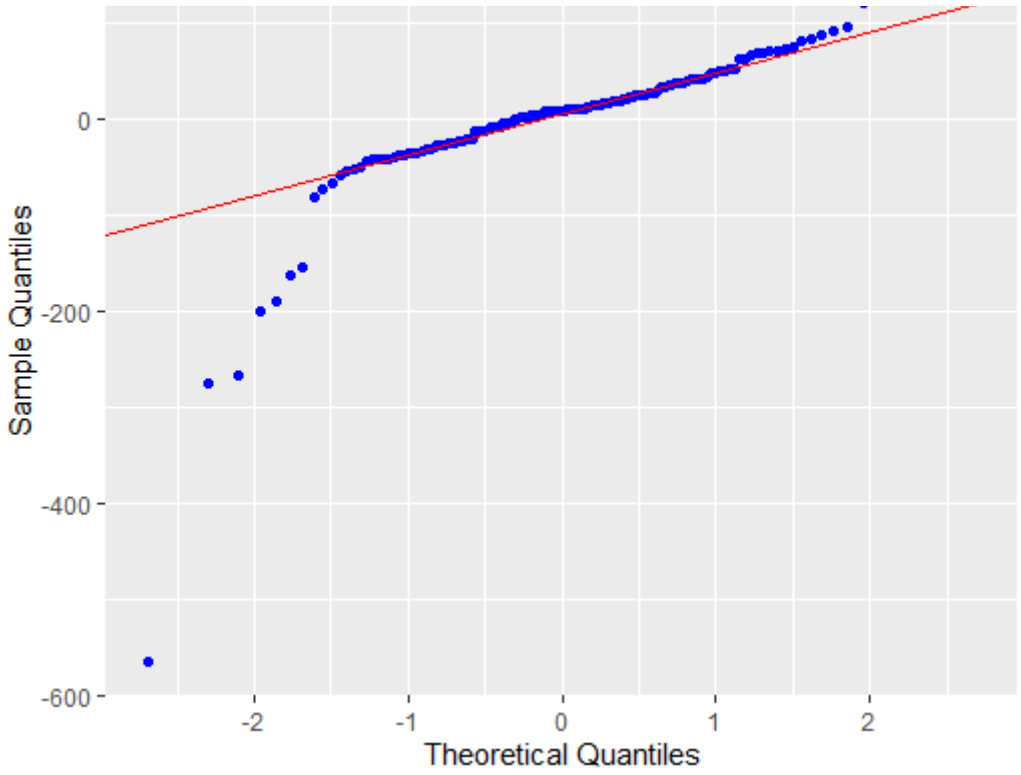


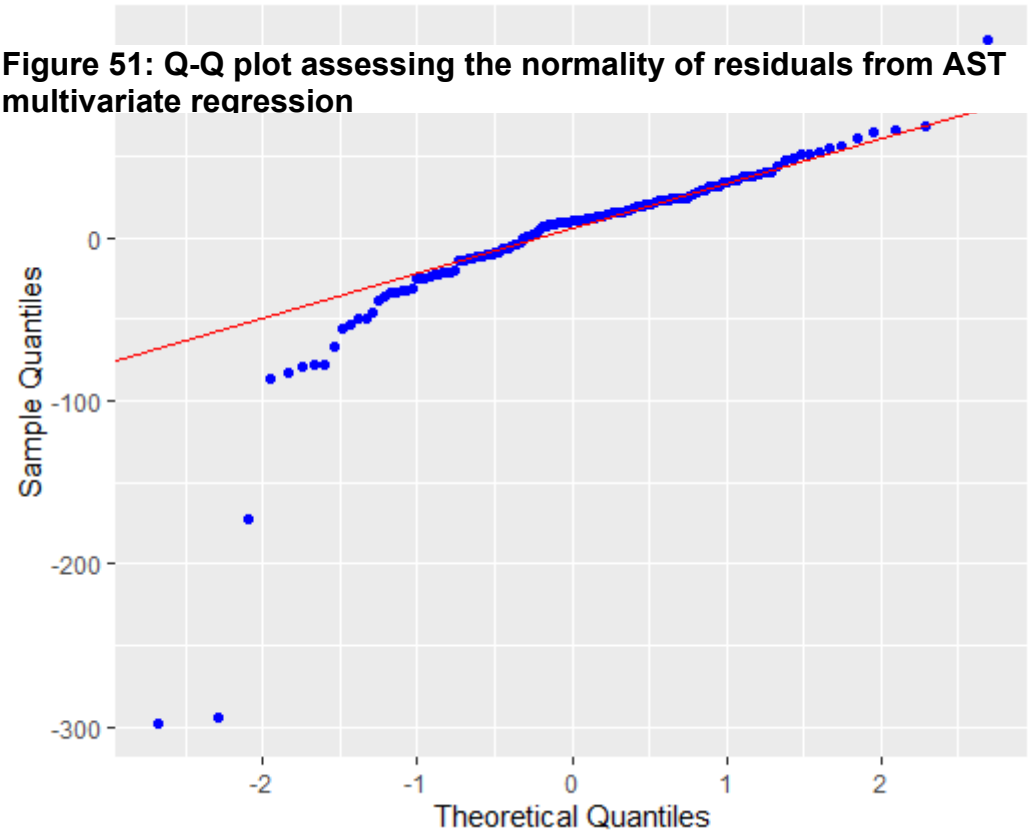
Table 102: Linear regression of change in ALT against study type, age, gender and lipodystrophy type

	Coefficient (ALT, U/L)	Standard error	p-value	Adjusted R^2
ATE of metreleptin with or without supportive care versus supportive care	-33.41	15.74	**0.036***	0.135
Abbreviations: ATE, Average treatment effect. * denotes significance at the p<0.05 level				

17.12.4.1.4 Mean U/L change in AST

The multivariate analysis results suggest that metreleptin with or without supportive care reduced AST by 20.9 U/L compared to supportive care. The results were not statistically significant (p=0.051; Table 103). A low adjusted R^2 (0.135), alongside a Q-Q plot (Figure 51) also supported our assumption that a

Figure 51: Q-Q plot assessing the normality of residuals from AST multivariate regression



regression model was not a good approximation of the covariates on the outcome of interest.

Table 103: Linear regression of change in AST against study type, age, gender and lipodystrophy type

	Coefficient (AST, U/L)	Standard error	p-value	Adjusted R^2
ATE of metreleptin with or without supportive care	-20.86	10.59	0.051	0.11
Abbreviations: ATE, Average treatment effect. * denotes significance at the p<0.05 level				

17.12.4.1.5 Pancreatitis (complete/case analysis)

The multivariate analysis results showed that the odds ratio (OR) of pancreatitis for metreleptin with or without supportive care compared to supportive care is 0.189, suggesting that pancreatitis is statistically less likely to occur when receiving metreleptin (p=0.031; Table 104). A low Nagelkerke R^2 (0.094) also indicates that the model has a low goodness of fit and that regression was not a good fit of the data.

Table 104: General linear model of incidence of pancreatitis at outcome timepoint against study type, age, gender and lipodystrophy type

	Coefficient	Odds ratio	Standard error	Nagelkerke pseudo R^2	p-value
ATE of metreleptin with or without supportive care versus supportive care	-1.665	0.189	0.770	0.094	**0.031***
Abbreviations: ATE, Average treatment effect * denotes significance at the p<0.05 level					

17.12.4.1.6 Pancreatitis (imputed)

The multivariate analysis based on imputation for missing data results showed that the odds ratio of pancreatitis for metreleptin with or without supportive care compared to supportive care is 0.169, demonstrating that pancreatitis is

statistically less likely to occur with metreleptin with or without supportive care (p=0.019; Table 105). The results are consistent with the complete case analysis. A low Nagelkerke R^2 (0.095) also indicates that the model has a low goodness of fit and that regression was not a good fit of the data.

Table 105: General linear model of incidence of pancreatitis (imputed in supportive care study) at outcome timepoint against study type, age, gender and lipodystrophy type

	Coefficient	**Odds ratio**	**Standard error**	**Nagelkerke pseudo R^2**	**p-value**
ATE of metreleptin with or without supportive care versus supportive care	-1.78	0.17	0.76	0.095	**0.019***
Abbreviations: ATE, Average treatment effect * denotes significance at the p<0.05 level					

17.12.4.1.7 Mortality

The multivariate analysis results showed no difference between the risk of mortality between metreleptin with or without supportive care and supportive care (HR: 1.299; p=0.479; Table 106)

Table 106: Cox regression model assessing mortality against study type, age, gender and lipodystrophy type

	Coefficient	**HR**	**Standard error**	**p-value**
ATE of metreleptin with or without supportive care versus supportive care	0.26	1.30	0.37	0.48
Abbreviations: ATE, Average treatment effect; HR, Hazard ratio * denotes significance at the p<0.05 level				

17.12.5 Covariate balance

The cobalt package in R was used to assess covariate balance after weighting. For each outcome, a summary of patient characteristics alongside density or probability plots for each covariate before and after weighting are provided. A summary of standardised mean differences; variance rations and KS-statistics are also provided before and after weighting.

17.12.5.1 HbA1c

17.12.5.1.1 Summary of patient characteristics

A summary of patient characteristics before and after weighting in the HbA1c outcome is given in

Table 107).

Table 107: A summary of patient characteristics before and after weighting in HbA1c change from baseline to Month 12

	Unweighted		**Stabilized weights**	
	Supportive care	**Metreleptin with or without supportive care**	**Supportive care**	**Metreleptin with or without supportive care**
N	21	101	13.59	25.17
Age, n (SD)	38.91 (15.93)	28.91 (15.92)	37.05 (16.17)	26.73 (16.33)
Gender, male (%)	5 (23.81%)	16 (15.84%)	2.2 (16.4%)	4.1 (16.3%)
Lipodystrophy type, partial (%)	18 (85.71%)	39 (38.61%)	11.2 (82.7%)	11.6 (26.2%)
Abbreviations: ATE, Average treatment effect; CI, Confidence interval * denotes significance at the p<0.05 level				

17.12.5.1.2 Density plots

Density plots suggested an improvement in covariate balance after weighting in the HbA1c outcome (Figure 52, Figure 53,Figure 54)

Figure 52: Lipodystrophy type distribution before and after IPW in HbA1c outcome using stabilized weights

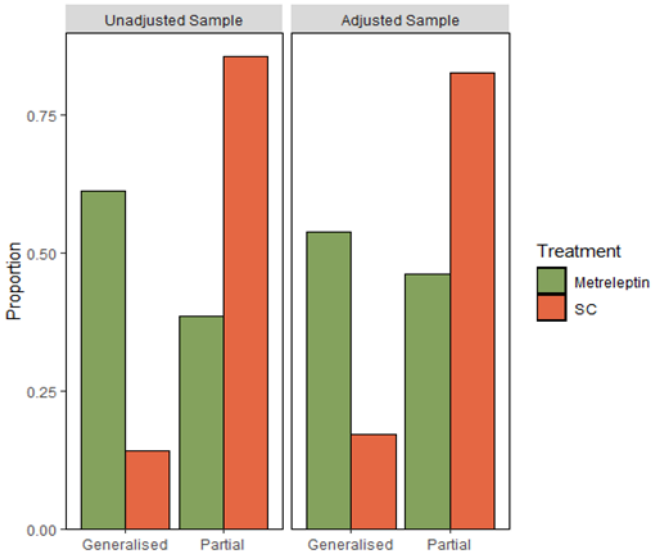


Figure 53: Distribution of age before and after IPW in HbA1c outcome using stabilized weights

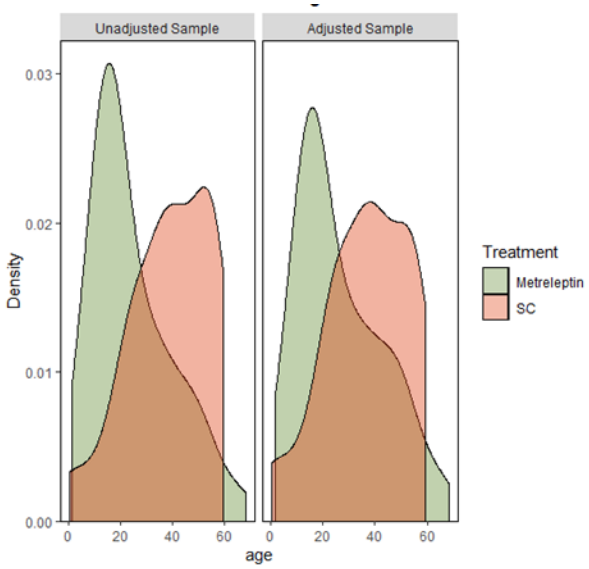
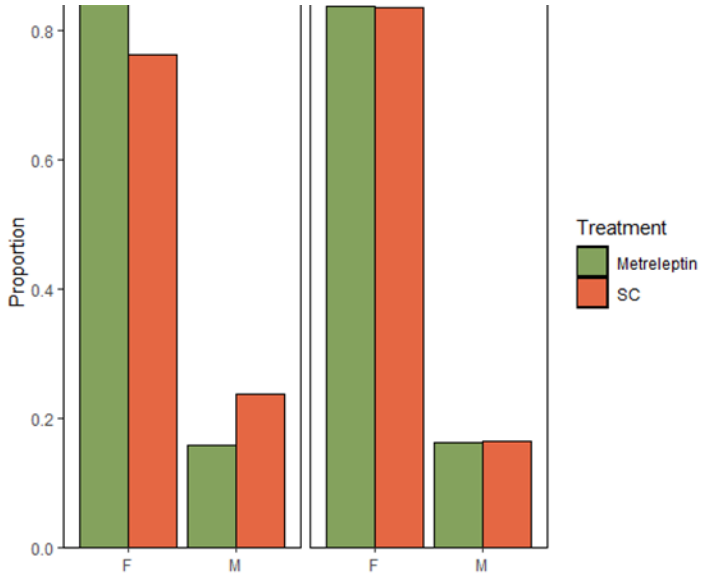


Figure 54: Distribution of gender before and after IPW in HbA1c outcome using stabilized weights



17.12.5.1.3 Statistical evaluation

An assessment of the standardized mean difference, variance ratio and Kolmogrov-Smirnov test suggest improvements in covariate balance in gender in the HbA1c outcome (Table 108).

Table 108: Statistical summary of covariate balance before and after IPW with stabilized weights in HbA1c outcome

	Unweighted						Stabilized weights					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.93	Not balanced	0.93	Balanced	0.50	Not balanced	-0.66	Not balanced	1.02	Balanced	0.33	Not balanced
Gender (male)	-0.08	Balanced					-0.0007	Balanced				
Lipodystrophy type (partial)	-0.47	Not balanced					-0.37	Not balanced				

Abbreviations: KS, Kolmogrov-Smirnov; SMD, Standardised mean difference; VR, Variance ratio.

17.12.5.2 Triglycerides

17.12.5.2.1 Summary of patient characteristics

A summary of patient characteristics before and after weighting in the triglyceride outcome is given in Table 109.

Table 109: A summary of patient characteristics before and after weighting in triglyceride change from baseline to Month 12

	Unweighted		**Weighted**	
	Supportive care	**Metreleptin with or without supportive care**	**Supportive care**	**Metreleptin with or without supportive care**
N	46	101	150	145
Age, n (SD)	26.68 (19.49)	24.23 (15.42)	24.18 (20.43)	25.42 (15.61)
Gender, male (%)	12 (26.09%)	16 (15.84%)	24.9 (16.6%)	25.2 (17.3%)
Lipodystrophy type, partial (%)	33 (71.74%)	39 (38.61%)	71.6 (47.8%)	70.3 (48.3%)
Abbreviations: ATE, Average treatment effect; CI, Confidence interval * denotes significance at the p<0.05 level				

17.12.5.2.2 Density plots

Density plots suggested an improvement in covariate balance after weighting in the triglyceride outcome (Figure 55, Figure 56, Figure 57)

Figure 56: Lipodystrophy type distribution before and after IPW in triglyceride outcome

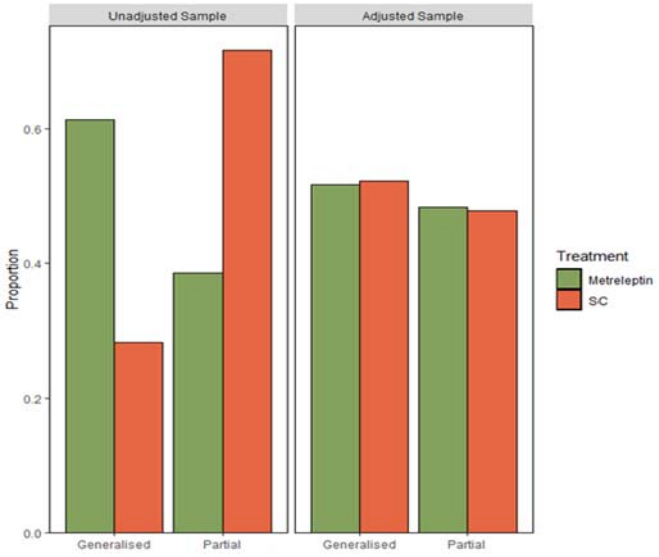


Figure 55: Distribution of age before and after IPW in triglyceride outcome

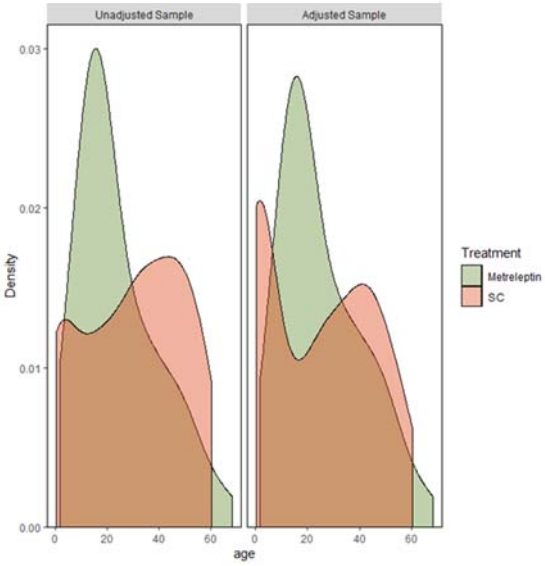
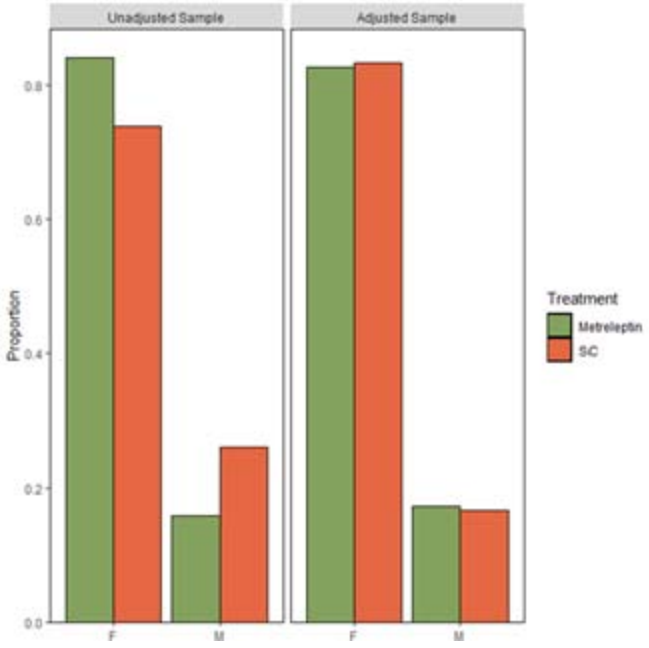


Figure 57: Distribution of gender before and after IPW in triglyceride outcome



17.12.5.2.3 Statistical evaluation

An assessment of the standardized mean difference, variance ratio and Kolmogrov-Smirnov test suggest improvements in the balance of all covariate balance after weighting in the triglyceride outcome (Table 110).

Table 110: Statistical summary of covariate balance before and after IPW in triglyceride outcome

	Unweighted						**Weighted**					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.31	Not balanced	0.63	Balanced	0.28	Not balanced	0.071	Balanced	0.58	Balanced	0.33	Not balanced
Gender (male)	-0.102	Not balanced					0.007	Balanced				
Lipodystrophy type (partial)	-0.331	Not balanced					0.005	Balanced				
Abbreviations: KS, Kolmogrov-Smirnov; SMD, Standardised mean difference; VR, Variance ratio.												

17.12.5.3 ALT

17.12.5.3.1 Summary of patient characteristics

A summary of patient characteristics before and after weighting in the ALT outcome is given in Table 111)

Table 111: A summary of patient characteristics before and after weighting in ALT change from baseline to Month 12

	Unweighted		**Weighted**	
	Supportive care	**Metreleptin with or without supportive care**	**Supportive care**	**Metreleptin with or without supportive care**
N	42	99	150	139
Age, n (SD)	30.99 (18.84)	24.38 (15.54)	25.02 (20.07)	25.90 (15.79)
Gender, male (%)	10 (23.80%)	16 (16.16%)	19.7 (13.2%)	22.6 (16.2%)
Lipodystrophy type, partial (%)	32 (76.19%)	38 (38.38%)	68.6 (46.0%)	67.8 (48.7%)
Abbreviations: ATE, Average treatment effect; CI, Confidence interval * denotes significance at the p<0.05 level				

17.12.5.3.2 Density plots

Density plots suggested an improvement in covariate balance after weighting in the ALT outcome (Figure 58, Figure 59 and Figure 60).

Figure 59: Lipodystrophy type distribution before and after IPW in ALT outcome

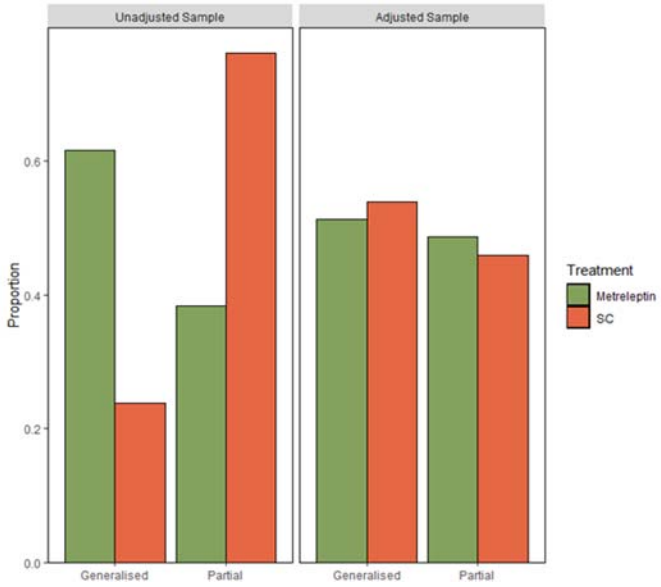


Figure 58: Distribution of age before and after IPW in ALT outcome

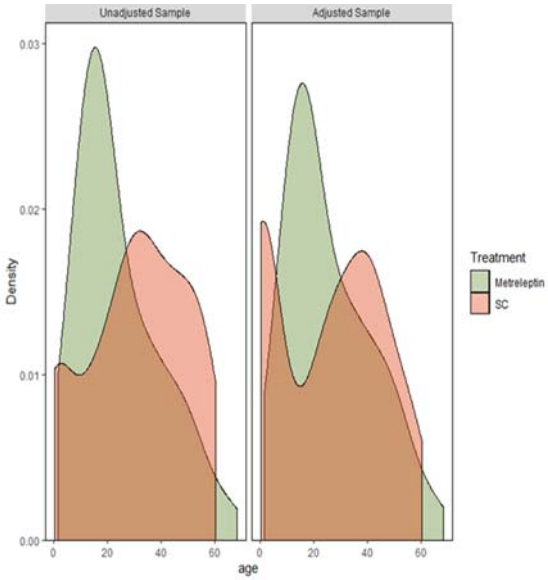
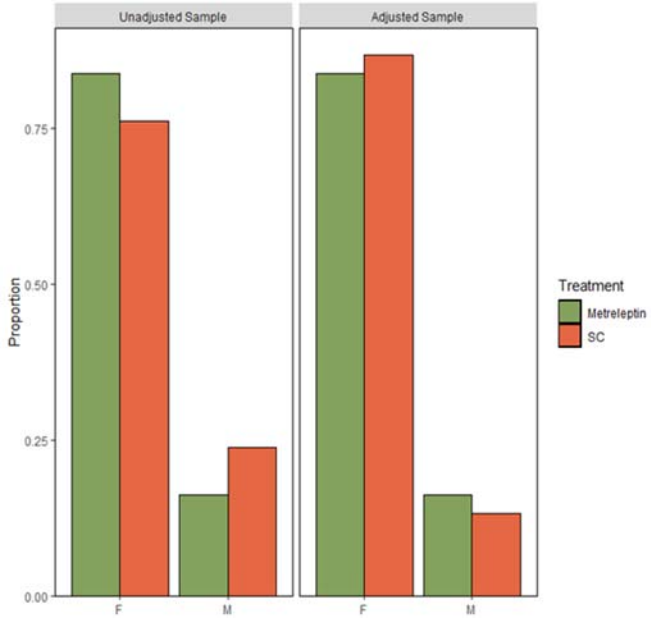


Figure 60: Distribution of gender before and after IPW in ALT outcome



17.12.5.3.3 Statistical evaluation

An assessment of the standardized mean difference, variance ratio and Kolmogrov-Smirnov test suggest improvements in the balance of all covariate balance after weighting in the ALT outcome (

Table 112).

	Unweighted						**Stabilized weights**					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.383	Not balanced	0.680	Balanced	0.327	Not balanced	0.051	Balanced	0.609	Balanced	0.327	Not balanced
Gender (male)	-0.077	Balanced					0.030	Balanced				
Lipodystrophy type (partial)	-0.378	Not balanced					0.027	Balanced				
Abbreviations: KS, Kolmogrov-Smirnov; SMD,Standardised mean difference; VR, Variance ratio.												

Table 112: Statistical summary of covariate balance before and after IPW in ALT outcome

	Unweighted						Stabilized weights					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.383	Not balanced	0.680	Balanced	0.327	Not balanced	0.051	Balanced	0.609	Balanced	0.327	Not balanced
Gender (male)	-0.077	Balanced					0.030	Balanced				
Lipodystrophy type (partial)	-0.378	Not balanced					0.027	Balanced				

Abbreviations: KS, Kolmogrov-Smirnov; SMD,Standardised mean difference; VR, Variance ratio.

17.12.5.4 AST

17.12.5.4.1 Summary of patient characteristics

A summary of patient characteristics before and after weighting in the AST outcome is given in Table 113.

Table 113: A summary of patient characteristics before and after weighting in AST change from baseline to Month 12

	Unweighted		**Weighted**	
	Supportive care	**Metreleptin with or without supportive care**	**Supportive care**	**Metreleptin with or without supportive care**
N	38	99	145	136
Age, n (SD)	29.50 (18.92)	24.38 (15.54)	25.09 (19.76)	25.46 (15.64)
Gender, male (%)	9 (23.68%)	16 (16.16%)	18.6 (12.9%)	22.2 (16.4%)
Lipodystrophy type, partial (%)	28 (73.68%)	38 (38.34%)	64.5 (44.5%)	64.2 (47.4%)
Abbreviations: ATE, average treatment effect; CI, confidence interval * denotes significance at the p<0.05 level				

17.12.5.4.2 Density plots

Density plots suggested an improvement in covariate balance after weighting in the AST outcome (Figure 61, Figure 62, Figure 63).

Figure 62: Lipodystrophy type distribution before and after IPW in AST outcome

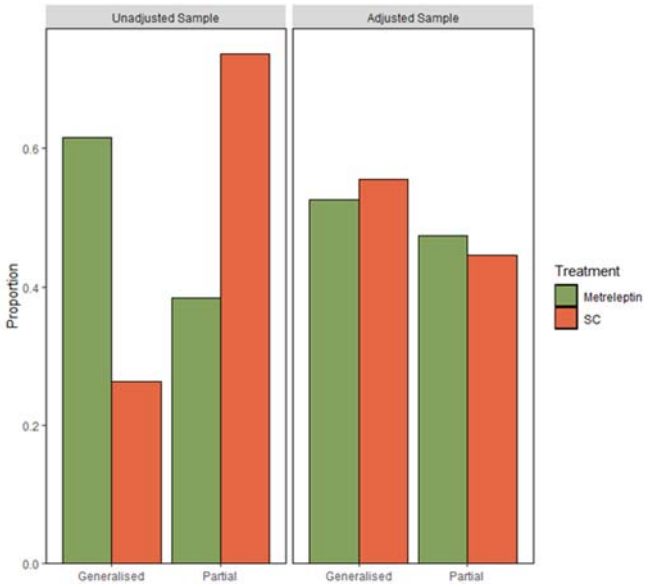


Figure 61: Distribution of age before and after IPW in AST outcome

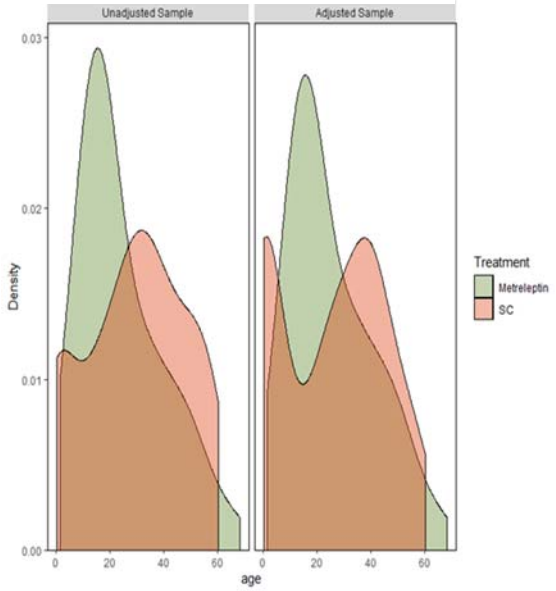
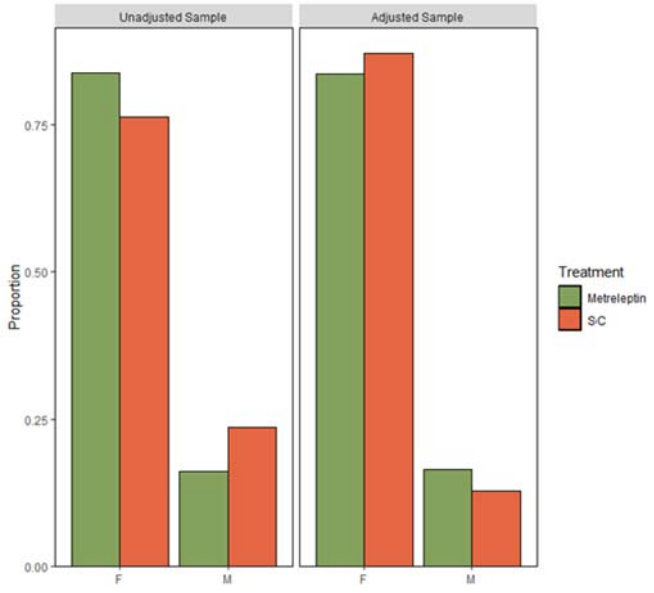


Figure 63: Distribution of gender before and after IPW in AST outcome



17.12.5.4.3 Statistical evaluation

An assessment of the standardized mean difference, variance ratio and Kolmogrov-Smirnov test suggest improvements in the balance of all covariate balance after weighting in the AST outcome (Table 114).

Table 114: Statistical summary of covariate balance before and after IPW in AST outcome

	Unweighted						**Stabilized weights**					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.296	Not balanced	0.675	Balanced	0.294	Not balanced	0.021	Balanced	0.617	Balanced	0.317	Not balanced
Gender (male)	-0.075	Balanced					0.036	Balanced				
Lipodystrophy type (partial)	-0.353	Not balanced					0.029	Balanced				

Abbreviations: KS, Kolmogrov-Smirnov; SMD, Standardised mean difference; VR, Variance ratio.

17.12.5.5 Pancreatitis

17.12.5.5.1 Summary of patient characteristics

A summary of patient characteristics before and after weighting in the pancreatitis outcome is given in Table 115.

Table 115: A summary of patient characteristics before and after weighting in incidence of pancreatitis

	Unweighted		**Weighted**	
	Supportive care	**Metreleptin with or without supportive care**	**Supportive care**	**Metreleptin with or without supportive care**
N	193	105	299	290
Age, n (SD)	26.71 (18.47)	24.30 (15.22)	25.86 (18.54)	25.38 (15.37)
Gender, male (%)	57 (29.53%)	16 (15.24%)	72.0 (24.1%)	58.7 (20.2%)
Lipodystrophy type, partial (%)	120 (62.18%)	41 (39.05%)	160.8 (53.7%)	151.2 (52.1%)
Abbreviations: ATE, average treatment effect; CI, confidence interval * denotes significance at the p<0.05 level				

17.12.5.5.2 Density plots

Density plots suggested an improvement in covariate balance after weighting in the pancreatitis outcome (Figure 64, Figure 65, Figure 66)

Figure 64: Lipodystrophy type distribution before and after IPW in pancreatitis outcome

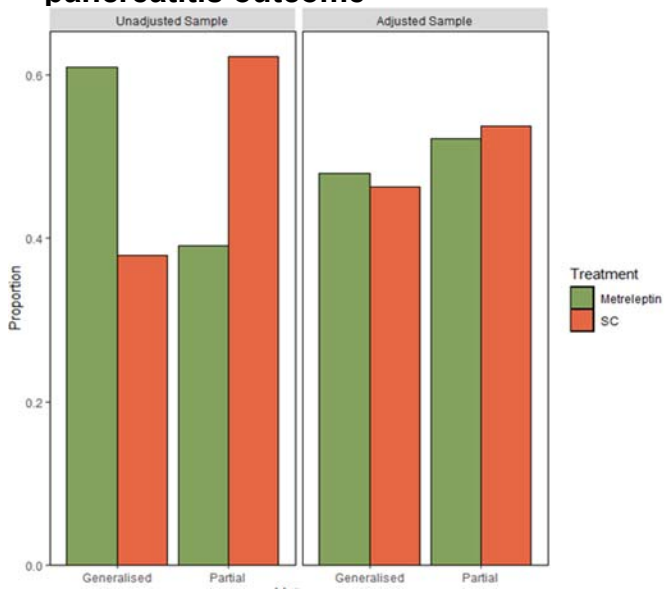


Figure 65: Distribution of age before and after IPW in pancreatitis outcome

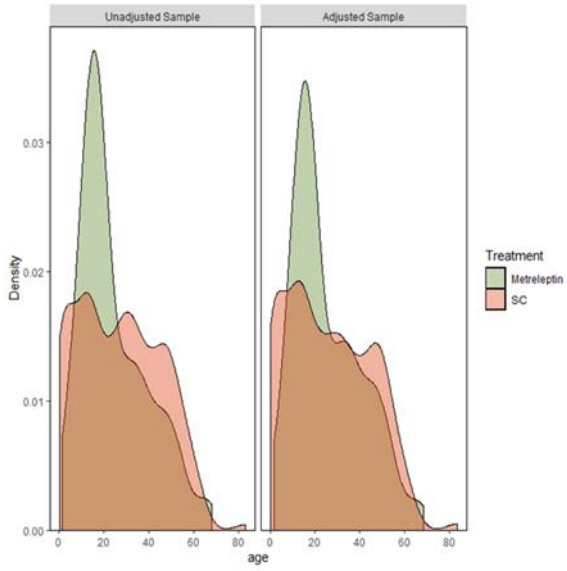
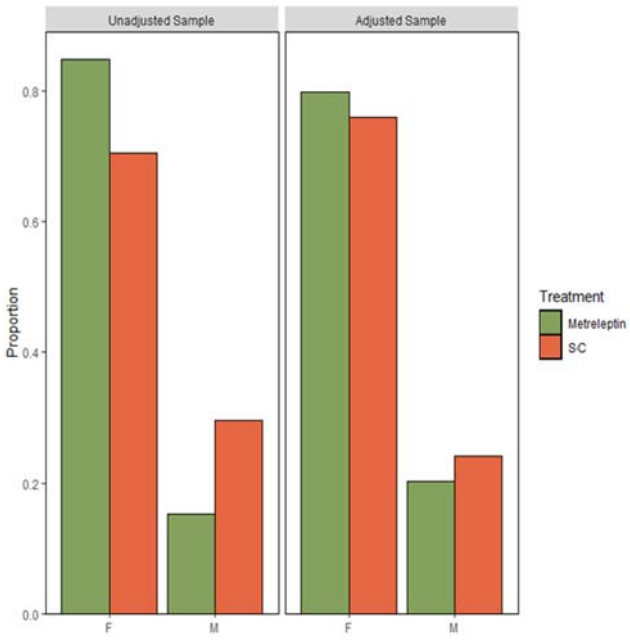


Figure 66: Distribution of gender before and after IPW in pancreatitis outcome



17.12.5.5.3 Statistical evaluation

An assessment of the standardized mean difference, variance ratio and Kolmogrov-Smirnov test suggest improvements in the balance of all covariate balance after weighting in the pancreatitis outcome (Table 116).

Table 116: Statistical summary of covariate balance before and after IPW in pancreatitis outcome

	Unweighted						**Stabilized weights**					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.1424	Not Balanced	0.6793	Balanced	0.1821	Not Balanced	-0.0280	Balanced	0.6876	Balanced	0.1590	Not Balanced
Gender (male)	-0.1430	Not Balanced					-0.0383	Balanced				
Lipodystrophy type (partial)	-0.2313	Not Balanced					-0.0160	Balanced				

Abbreviations: KS, Kolmogrov-Smirnov; SMD, standardised mean difference; VR, variance ratio.

17.12.5.6 Pancreatitis (with imputation)

17.12.5.6.1 Summary of patient characteristics

A summary of patient characteristics before and after weighting in the pancreatitis outcome when missing data is imputed is given in Table 117.

Table 117: A summary of patient characteristics before and after weighting in incidence of pancreatitis (with imputation)

	Unweighted		**Weighted**	
	Supportive care	**Metreleptin with or without supportive care**	**Supportive care**	**Metreleptin with or without supportive care**
N	228	105	334	321
Age, n (SD)	26.21 (18.37)	24.30 (15.22)	25.66 (18.55)	25.36 (15.19)
Gender, male (%)	68 (29.82%)	16 (15.24%)	82.9 (24.8%)	62.6 (19.5%)
Lipodystrophy type, partial (%)	149 (63.35%)	41 (39.05%)	190.0 (56.8%)	176.6 (55.0%)
Abbreviations: ATE, average treatment effect; CI, confidence interval * denotes significance at the p<0.05 level				

17.12.5.6.2 Density plots

Density plots suggested an improvement in covariate balance after weighting in the pancreatitis outcome (Figure 67, Figure 68, Figure 69)

Figure 68: Lipodystrophy type distribution before and after IPW in imputed pancreatitis outcome

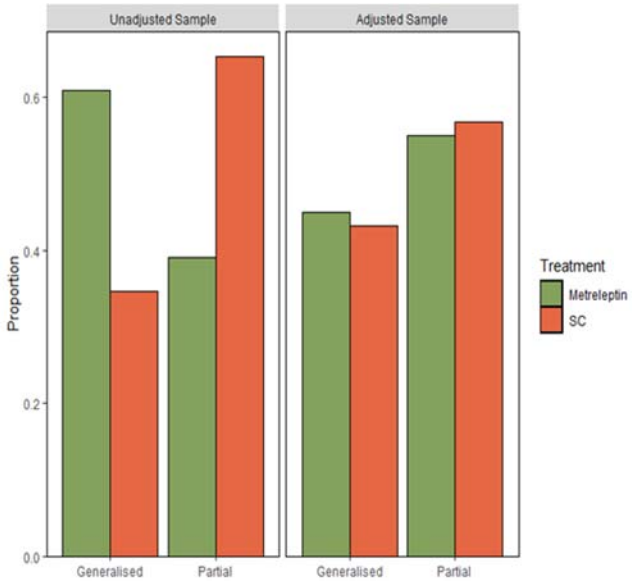


Figure 67: Distribution of age before and after IPW in imputed pancreatitis

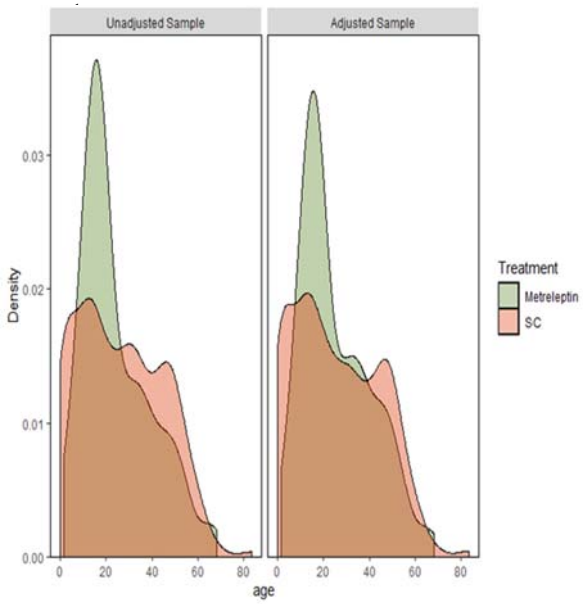
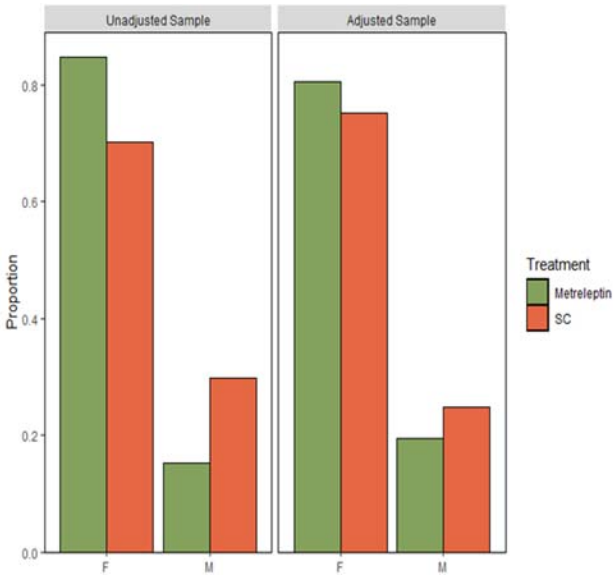


Figure 69: Distribution of gender before and after IPW in pancreatitis outcome



17.12.5.6.3 Statistical evaluation

An assessment of the standardized mean difference, variance ratio and Kolmogrov-Smirnov test suggest improvements in the balance of all covariate balance after weighting in the pancreatitis outcome when missing data was imputed (Table 117**Table 116**).

Table 118: Statistical summary of covariate balance before and after IPW in pancreatitis outcome

	Unweighted						**Stabilized weights**					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.1135	Not Balanced	0.6866	Balanced	0.1556	Not Balanced	-0.0181	Balanced	0.6714	Balanced	0.1621	Not Balanced
Gender (male)	-0.1459	Not Balanced					-0.0531	Balanced				
Lipodystrophy type (partial)	-0.2630	Not Balanced					-0.0184	Balanced				

17.12.5.7 Mortality

17.12.5.7.1 Summary of patient characteristics

A summary of patient characteristics before and after weighting in the mortality outcome is given in Table 119,.

Table 119: A summary of patient characteristics before and after weighting in all-cause mortality

	Unweighted		**Weighted**	
	Supportive care	**Metreleptin with or without supportive care**	**Supportive care**	**Metreleptin with or without supportive care**
N	228	106	335	322
Age, n (SD)	26.21 (18.37)	24.21 (15.18)	25.63 (18.55)	25.33 (15.17)
Gender, male (%)	68 (29.82%)	16 (15.09%)	82.9 (24.7%)	62.5 (19.4%)
Lipodystrophy type, partial (%)	149 (63.35%)	41 (38.68%)	190.0 (56.6%)	176.6 (54.8%)
Abbreviations: ATE, average treatment effect; CI, confidence interval * denotes significance at the p<0.05 level				

17.12.5.7.2 Density plots

Density plots suggested an improvement in covariate balance after weighting in the pancreatitis outcome (Figure 71, Figure 72)

Figure 70 :Lipodystrophy type distribution before and after IPW in mortality outcome

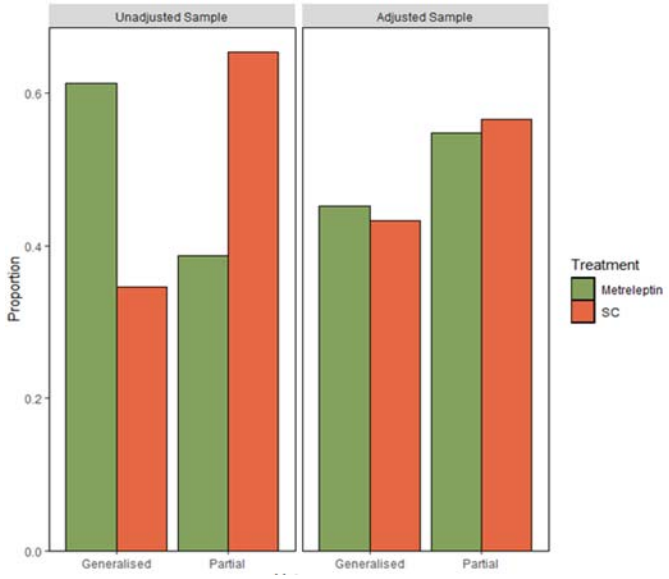


Figure 71: Distribution of age before and after IPW in mortality outcome

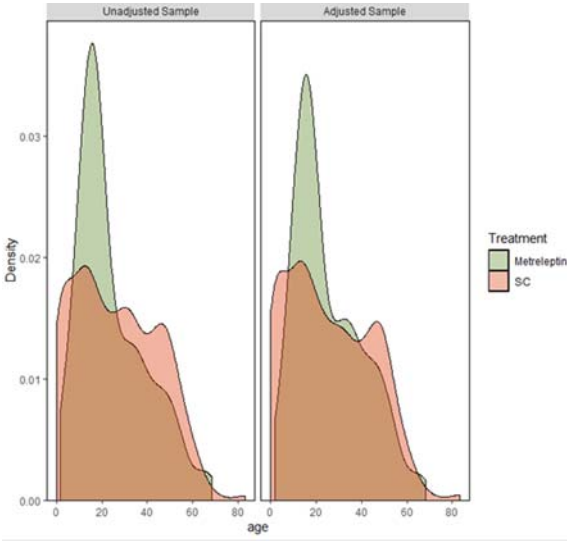
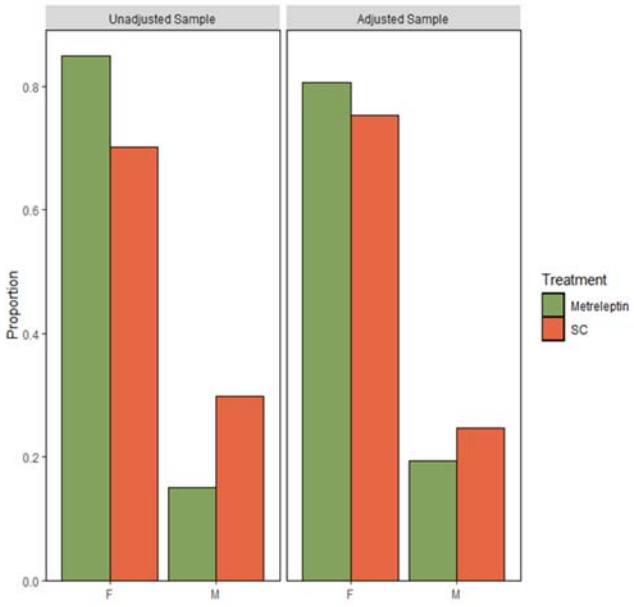


Figure 72: Distribution of gender before and after IPW in mortality outcome



17.12.5.7.3 Statistical evaluation

An assessment of the standardized mean difference, variance ratio and Kolmogrov-Smirnov test suggest improvements in the balance of all covariate balance after weighting in the mortality outcome (Table 120)

Table 120: Statistical summary of covariate balance before and after IPW in mortality outcome

	Unweighted						**Weighted**					
	SMD	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**	**SMD**	**SMD suggest balance?**	**VR**	**VR suggest balance?**	**KS**	**KS suggest balance?**
Age	-0.1189	Not Balanced	0.6824	Balanced	0.1591	Not Balanced	-0.0183	Balanced	0.67	Balanced	0.1629	Not Balanced
Gender (male)	-0.1473	Not Balanced					-0.0531	Balanced				
Lipodystrophy type (partial)	-0.2667	Not Balanced					-0.0184	Balanced				

17.13 Appendix 13: Cost effectiveness model

17.13.1 Costs

Table 121: Baseline medication by class

Baseline Medication	GL (N=66)	PL subgroup* (N=31)
Antidiabetic medication		
Any insulin	39	17
Biguanides	31	17
Thiazolidinediones	2	12
Sulfonylureas	0	5
Lipid lowering therapies		
HMG CoA Reductase inhibitors	11	12
Other lipid modifying agents	10	15
Fibrates	25	17
Other concomitant medications (antihypertensives)		
Lisinopril	9	7
Enalapril	7	3

*PL subgroup= patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L. All calculations for PL group are based on PL subgroup baseline medications

Table 122: Baseline medication as determined by prescription cost data 2018

Baseline Medication	GL (N=66)	PL (N=31)
Any insulin	39	17
Metformin	31	17
Pioglitazone	2	12
Gliclazide	0	5
Atorvastatin	11	12
Colesevelam	10	15
Bezalip Mono	25	17
Lisinopril	9	7
Enalapril	7	3

Insulin mix

Patients receiving insulin were assumed to be prescribed, in equal proportion, either:

- Long acting insulin and fast acting insulin separately (70:30 ratio assumed)
- Intermediate acting insulin and fast acting insulin separately (70:30 ratio assumed)
- Intermediate or long acting insulin with fast acting insulin as a combination formulation.

As per the methodology employed for other medication classes in the model, prescription cost data was used to identify the most commonly prescribed insulins for the insulin formulations listed above. A weighted average cost per unit of insulin was then calculated for use in the model.

Table 123: Insulin cost per unit

Insulin formulation	Drug tariff pack	Drug tariff cost	Cost/unit
Novorapid Flexpen 100u/ml	5 x 3ml pens	£30.60	£0.02
Novomix30 Flexpen 100u/ml	5 x 3ml pens	£29.89	£0.02
Humulin I kwikpen 100u/ml	5 x 3ml pens	£21.70	£0.01
Lantus solostar pen 100u/ml	5 x 3ml pens	£37.77	£0.03

Table 124: Weighted average cost per unit of insulin

Insulin formulation	Average cost per unit
Humulin I Kwikpen with Novorapid Flexpen (70:30 ratio assumed)	£0.016
Lantus solostar pen with Novorapid Flexpen (70:30 ratio assumed)	£0.024
Novomix 30 Flexpen	£0.020
Weighted cost per unit	**£0.019973**

Table 125: Dose-dependent daily medication cost

	Dose GL	Dose PL	Drug tariff pack	Drug tariff cost	Daily cost GL	Daily cost PL
Insulin	625 units	278 units	See insulin calc above	See insulin calc above	£12.48	£5.55
Metformin	500 mg/day	500 mg/day	28 x 500 mg tabs	£1.18	£0.04	£0.04
Pioglitazone	30 mg/day	30 mg/day	28 x 30 mg tabs	£1.68	£0.06	£0.06
Gliclazide	80 mg/day	80 mg/day	28 x 80 mg tabs	£0.99	£0.04	£0.04

Atorvastatin	20 mg/day	20 mg/day	28 x 20 mg tabs	£0.99	£0.04	£0.04
Colesevelam	2500 mg/day	2500 mg/day	180 x 625 mg tabs	£115.32	£2.56	£2.56
Bezalip-Mono	400 mg/day	400 mg/day	30 x 400 mg tabs	£7.63	£0.25	£0.25
Lisinopril	20 mg/day	20 mg/day	28 x 20 mg tabs	£0.98	£0.04	£0.04
enalapril	20 mg/day	20 mg/day	28 x 20 mg tabs	£2.14	£0.08	£0.08

Table 126: Baseline daily medication cost for study cohort

Baseline Medication	**GL (N=66)**	**PL (N=31)**
Any insulin	£486.84	£94.39
Metformin	£1.31	£0.72
Pioglitazone	£0.12	£0.72
Gliclazide	£0.00	£0.18
Atorvastatin	£0.39	£0.42
Colesevelam	£25.63	£38.44
Bezalip Mono	£6.36	£4.32
Lisinopril	£0.32	£0.25
Enalapril	£0.54	£0.23
Total cohort cost	**£521.49**	**£139.67**

Table 127: Baseline medication costs per patient

	GL	**PL**
Average daily cost per patient	£7.90	£4.51
Average annual cost per patient	£2,886.00	£1,645.61

Table 128: Proportion of patients able to stop medication

Baseline Medication	**GL**	**PL**
Any insulin	40%	5%
Metformin	0%	0%
Pioglitazone	52%	50%
Gliclazide	52%	50%
*Atorvastatin	0%	0%
*Colesevelam	0%	0%
Bezalip Mono	61%	51%
Lisinopril	17%	14%
Enalapril	17%	14%

* Delphi Panel concluded that only triglyceride-lowering medications (i.e. fibrates) would be discontinued or recued.

Table 129: Proportion of patients able to reduce medication

Baseline Medication	GL	PL
Any insulin	60%	50%
Metformin	48%	35%
Pioglitazone	48%	35%
Gliclazide	48%	35%
*Atorvastatin	0%	0%
*Colesevelam	0%	0%
Bezalip Mono	39%	23%
Lisinopril	12%	10%
Enalapril	12%	10%

* Delphi Panel concluded that only triglyceride-lowering medications (i.e. fibrates) would be discontinued or recued.

Table 130: Daily cost per medication for patients able to reduce dose

Medication	Initial daily cost per GL patient	Dose reduction *	Post-metreleptin daily cost per GL patient	Initial daily cost per PL patient	Dose reduction*	Post-metreleptin daily cost per PL patient
Insulin	£12.48	68%	£3.99	£5.55	50%	£2.78
metformin	£0.04	62%	£0.02	£0.04	50%	£0.02
pioglitazone	£0.06	62%	£0.02	£0.06	50%	£0.03
Gliclazide	£0.04	62%	£0.01	£0.04	50%	£0.02
atorvastatin	£0.04	0%	£0.04	£0.04	0%	£0.04
Colesevelam	£2.56	0%	£2.56	£2.56	0%	£2.56
Bezalip-Mono	£0.25	71%	£0.07	£0.25	54%	£0.12
Lisinopril	£0.04	32%	£0.02	£0.04	31%	£0.02
Enalapril	£0.08	32%	£0.05	£0.08	31%	£0.05

*Assumed linear relationship between dose and costs

Table 131: Expected post-metreleptin daily medication costs for study cohort

Baseline Medication	GL (N=66)	PL (N=31)
Any insulin	£93.47	£66.08
Metformin	£0.92	£0.59
Pioglitazone	£0.02	£0.23

Gliclazide	£0.00	£0.06
Atorvastatin	£0.39	£0.42
Colesevelam	£25.63	£38.44
Bezalip Mono	£0.72	£1.58
Lisinopril	£0.25	£0.20
Enalapril	£0.42	£0.19
Total cohort cost	**£121.82**	**£107.80**

Table 132: Expected post-metreleptin medication costs per patient

	GL	**PL**
Average daily cost per patient	£1.85	£3.48
Average annual cost per patient	£674.17	£1,270.09

17.13.2 One-way sensitivity analysis variables

Table 133: Variables used in One-way sensitivity analysis

Variable	Mean base-case value	Mean lower-bound	Mean upper-bound
Age GL male	19.50	15.60	23.40
Age GL female	17.30	13.84	20.76
Age PL male	37.00	29.60	44.40
Age PL female	37.00	29.60	44.40
% Female GL	0.77	0.62	0.93
% Female PL	0.97	0.77	1.16
weight GL male	55.10	44.08	66.12
weight GL female	51.90	41.52	62.28
weight PL male	68.70	54.96	82.44
weight PL female	68.70	54.96	82.44
GL hba1c baseline M	8.10	6.48	9.72
GL hba1c baseline F	8.80	7.04	10.56
PL hba1c baseline	8.80	7.04	10.56
hba1c change GL	-2.20	-1.7600	-2.6400
hba1c change PL	-0.90	-0.720	-1.080
Trig baselineGL	2299.38	1840	2759
Trig baseline PL	2299.38	1840	2759
trig_adj GL	-915.30	-1358	-472
trig_adj PL	-915.30	-732	-1098
trig_adj nmol	-10.34	-8	-12
insulin reduction GL	0.50	0.40	0.60
insulin reduction PL	0.50	0.40	0.60
Carers per patient	2.00	1.60	2.40
carer disutility	-0.10	-0.08	-0.12
Relative risk of Liver complications for metreleptin vs SC for GL patients	0.23	0.18	0.28
Relative risk of Liver complications for metreleptin vs SC for PL patients	0.75	0.60	0.90
Transition probabilities			
Asymptomatic liver disease to Advanced fibrosis	0.0533	0.0426	0.0639
Advanced fibrosis to Asymptomatic liver disease	0.1057	0.0846	0.1269
Advanced fibrosis to Compensated cirrhosis	0.0555	0.0444	0.0667
Compensated cirrhosis to Compensated cirrhosis with varices	0.0604	0.0483	0.0725
Compensated cirrhosis to Decompensated cirrhosis	0.0703	0.0563	0.0844
Decompensated cirrhosis to Decompensated cirrhosis with varices	0.1266	0.1013	0.1519

Decompensated cirrhosis to transplant	0.0228	0.0183	0.0274
Compensated cirrhosis with varices to decompensated cirrhosis with varices	0.0703	0.0563	0.0844
Compensated cirrhosis with varices to Bleeding	0.1209	0.0967	0.1451
Compensated cirrhosis with varices to HCC	0.0264	0.0211	0.0317
Decompensated cirrhosis with varices to Bleeding	0.3163	0.2531	0.3796
Decompensated cirrhosis with varices to HCC	0.0329	0.0263	0.0395
Decompensated cirrhosis with varices to transplant	0.0228	0.0183	0.0274
Bleeding to HCC	0.0369	0.0295	0.0442
Bleeding to transplant	0.0256	0.0205	0.0307
HCC to transplant	0.0408	0.0326	0.0489
Asymptomatic liver disease to Death	0.0000	0.0000	0.0000
Advanced fibrosis to Death	0.0060	0.0048	0.0072
Compensated cirrhosis to Death	0.0219	0.0175	0.0263
Decompensated cirrhosis to Death	0.2150	0.1720	0.2580
Compensated cirrhosis with varices to Death	0.0219	0.0175	0.0263
Decompensated cirrhosis with varices to Death	0.2150	0.1720	0.2580
Bleeding to Death	0.2994	0.2395	0.3593
HCC to Death	0.5604	0.4483	0.6725
Liver transplant to Death	0.1810	0.1448	0.2172
Post liver Transplant to Death	0.0435	0.0348	0.0522
No CVD to Myocardial infarction	0.0113	0.0091	0.0136
No CVD to Angina	0.0060	0.0048	0.0072
No CVD to Congestive heart failure	0.0026	0.0021	0.0031
No CVD to Stroke	0.0015	0.0012	0.0018
Angina to MI	0.0113	0.0091	0.0136
Angina to CHF	0.0026	0.0021	0.0031
Angina to stroke	0.0015	0.0012	0.0018
Post myocardial infarction to Congestive heart failure	0.0224	0.0179	0.0269
Myocardial Infarction to Death	0.0713	0.0571	0.0856
Post myocardial infarction to Death	0.0286	0.0229	0.0343
Congestive heart failure to Death	0.4300	0.3440	0.5160
Stroke to Death	0.0690	0.0552	0.0828
Post-stroke to Death	0.2360	0.1888	0.2832

No CKD to Microalbuminuria	0.0436	0.0349	0.0523
No CKD to macroalbuminuria	0.0037	0.0030	0.0044
No CKD to end stage renal disease	0.0008	0.0006	0.0010
Microalbuminuria to macroalbuminuria	0.1566	0.1253	0.1879
Microalbuminuria to end stage renal disease	0.0515	0.0412	0.0619
Macroalbuminuria to end stage renal disease	0.4334	0.3468	0.5201
End stage renal disease to transplant 18-34	0.1520	0.1216	0.1824
End stage renal disease to transplant 35-44	0.1350	0.1080	0.1620
End stage renal disease to transplant 45-54	0.1140	0.0912	0.1368
End stage renal disease to transplant 55-64	0.0750	0.0600	0.0900
End stage renal disease to transplant 65+	0.0390	0.0312	0.0468
End stage renal disease to death	0.0884	0.0707	0.1061
Macroalbuminuria to death	0.0070	0.0056	0.0084
Microalbuminuria to death	0.0004	0.0003	0.0005
No CKD to death	0.0000	0.0000	0.0000
No retinopathy to Background retinopathy	0.0454	0.0363	0.0545
No retinopathy to Proliferative retinopathy	0.0013	0.0010	0.0016
No retinopathy to Macular Oedema	0.0012	0.0010	0.0014
No retinopathy to Blindness	0.0000	0.0000	0.0000
Background retinopathy to Proliferative retinopathy	0.0595	0.0476	0.0714
Background retinopathy to Macular Oedema	0.0512	0.0410	0.0614
Background retinopathy to Blindness	0.0001	0.0001	0.0001
Proliferative retinopathy to Blindness	0.0038	0.0030	0.0046
Macular Oedema to Blindness	0.0016	0.0013	0.0019
No Neuropathy to Peripheral Neuropathy	0.0512	0.0409	0.0614
No Neuropathy to Amputation	0.0004	0.0004	0.0005
Peripheral Neuropathy to Amputation	0.0225	0.0180	0.0270
Risk of pancreatitis in patients treated with SC alone	[redacted]	[redacted]	[redacted]
Risk of pancreatitis in patients treated with metreleptin	[redacted]	[redacted]	[redacted]
Pancreatitis to death	0.2000	0.1600	0.2400

Costs and metreleptin dose			
GL Discont. noncompliance - 1 year	1.50%	0.0120	0.0180
GL Discont. noncompliance - 2-5 years	1.50%	0.0120	0.0180
GL Discont. noncompliance - 10 years+	1.50%	0.0120	0.0180
PL Discont. noncompliance - 1 year	3.86%	0.0309	0.0463
PL Discont. noncompliance - 2-5 years	3.86%	0.0309	0.0463
PL Discont. noncompliance - 10 years+	3.86%	0.0309	0.0463
Proportion of patients without dose escalation	26%	0.2088	0.3132
Proportion of patients escalating to max dose	13%	0.1040	0.1560
Year 1 disease management cost for patients treated with metreleptin	976.38	781.10	1171.66
Year 2+ disease management costs for patients treated with metreleptin	325.46	260.37	390.55
Year 1 disease management costs for patients treated with SC	325.46	260.37	390.55
Year 2+ disease management costs for patient treated with SC only	325.46	260.37	390.55
Cost of SC medication for GL patient treated with metreleptin	674.17	539.34	809.00
Cost of SC medication for GL patients treated with SC alone	2886.00	2308.80	3463.20
Cost of SC medication for PL patient treated with metreleptin	1270.09	1016.07	1524.11
Cost of SC medication for PL patient treated with SC alone	1645.61	1316.49	1974.73
Cost Angina year 1	6854.89	5483.91	8225.87
Cost Angina year 2+	308.55	246.84	370.25
Cost stroke year 1	4461.79	3569.43	5354.14
Cost stroke year 2+	165.87	132.69	199.04
Cost congestive heart failure year 1	3847.55	3078.04	4617.06
Cost congestive heart failure year 2+	2779.05	2223.24	3334.86
Cost myocardial infarction year 1	3992.55	3194.04	4791.06
Cost myocardial infarction year 2+	843.24	674.59	1011.89
Cost microalbuminuria	39.35	31.48	47.22
Cost macroalbuminuria	4026.03	3220.82	4831.23

Cost end stage renal disease	5632.97	4506.38	6759.57
Cost kidney transplant year 1	22043.99	17635.19	26452.79
Cost kidney transplant year 2+	8233.09	6586.47	9879.71
Cost asymptomatic liver disease	143.39	114.71	172.07
Cost advanced fibrosis	462.28	369.83	554.74
Cost compensated cirrhosis	462.28	369.83	554.74
Cost decompensated cirrhosis	13901.68	11121.35	16682.02
Cost compensated cirrhosis with varices	462.28	369.83	554.74
Cost decompensated cirrhosis with varices	13901.68	11121.35	16682.02
Cost bleeding	2839.18	2271.35	3407.02
Cost HCC	13901.68	11121.35	16682.02
Cost liver transplant year 1	63295.43	50636.34	75954.51
Cost liver transplant year 2	19659.40	15727.52	23591.28
Cost Liver transplant year 3+	8984.63	7187.71	10781.56
Cost pancreatitis episode	1174.11	939.29	1408.93
Cost background retinopathy	308.42	246.74	370.10
Cost proliferative retinopathy	1050.49	840.39	1260.59
Cost macular oedema	3059.64	2447.71	3671.57
Cost blindness year 1	5974.42	4779.54	7169.30
Cost blindness year 2+	5772.24	4617.79	6926.69
Cost neuropathy	386.81	309.45	464.18
Cost amputation year 1	6090.60	4872.48	7308.72
Cost amputation year 2+	0.00	0.00	0.00
Health state utility decrements			
Decrement angina	-0.09	-0.05	-0.13
Decrement stroke	-0.16	-0.11	-0.22
Decrement congestive heart failure	-0.11	-0.05	-0.17
Decrement myocardial infarction	-0.06	-0.04	-0.07
Decrement microalbuminuria	0.00	0.00	0.00
Decrement macroalbuminuria	-0.05	-0.04	-0.06
Decrement end stage renal disease	-0.22	-0.18	-0.27
Decrement kidney transplant year 1	-0.15	-0.12	-0.18
Decrement kidney transplant year 2+	-0.08	-0.07	-0.10
Decrement asymptomatic liver disease	-0.03	-0.02	-0.04
Decrement advanced fibrosis	-0.15	-0.12	-0.18
Decrement compensated cirrhosis	-0.27	-0.22	-0.32

Decrement decompensated cirrhosis	-0.33	-0.26	-0.40
Decrement compensated cirrhosis with varices	-0.27	-0.22	-0.32
Decrement decompensated cirrhosis with varices	-0.33	-0.26	-0.40
Decrement bleeding	-0.33	-0.26	-0.40
Decrement hepatocellular carcinoma	-0.33	-0.26	-0.40
Decrement liver transpant year 1	-0.07	-0.06	-0.08
Decrement liver transplant year 2+	-0.02	-0.02	-0.02
Decrement pancreatitis	-0.13	-0.10	-0.16
Decrement background retinopathy	-0.03	-0.02	-0.03
Decrement proliferative retinopathy	-0.07	-0.04	-0.10
Decrement macular oedema	-0.04	-0.01	-0.07
Decrement blindness	-0.07	-0.05	-0.12
Decrement neuropathy	-0.08	-0.17	-0.11
Decrement amputation	-0.28	-0.17	-0.39
Utility <18	0.93	0.74	1.00
Utility 18-24	0.93	0.74	1.00
Utility 25-34	0.92	0.74	1.00
Utility 35-44	0.89	0.71	1.00
Utility 45-54	0.86	0.68	1.00
Utility 55-64	0.81	0.65	0.97
Utility 65-74	0.77	0.62	0.93
Utility 75+	0.70	0.56	0.84

17.13.3 Probabilistic sensitivity analysis variables

Table 134: Variables used in probabilistic sensitivity analysis

Variable	Mean base-case value	Standard error	Distribution
Age GL male	19.50	4.6734	GAMMA
Age GL female	17.30	1.4885	GAMMA
Age PL male	37.00	2.5809	GAMMA
Age PL female	37.00	2.5809	GAMMA
% Female GL	0.77	0.0455	BETA
% Female PL	0.97	0.0065	BETA
weight GL male	55.10	5.2208	GAMMA
weight GL female	51.90	2.6017	GAMMA

weight PL male	68.70	2.6348	GAMMA
weight PL female	68.70	2.6348	GAMMA
GL hba1c baseline M	8.10	0.6507	GAMMA
GL hba1c baseline F	8.80	0.3151	GAMMA
PL hba1c baseline	8.80	0.3377	GAMMA
hba1c change GL	-2.20	0.2799	GAMMA
hba1c change PL	-0.90	0.2367	GAMMA
Trig baselineGL	2299.38	47.9518	GAMMA
Trig baseline PL	2299.38	47.9518	GAMMA
trig_adj GL	-915.30	225.9500	GAMMA
trig_adj PL	-915.30	225.9500	GAMMA
trig_adj nmol	-10.34	2.5500	GAMMA
insulin reduction GL	0.50	0.1000	BETA
insulin reduction PL	0.50	0.1000	BETA
Carers per patient	2.00	0.4000	GAMMA
carer disutility	-0.10	-0.0197	GAMMA
Relative risk of Liver complications for metreleptin vs SC for GL patients	0.23	4.6734	GAMMA
Relative risk of Liver complications for metreleptin vs SC for PL patients	0.75	1.4885	GAMMA
Transition probabilities			
Asymptomatic liver disease to Advanced fibrosis	0.0533	0.0107	BETA
Advanced fibrosis to Asymptomatic liver disease	0.1057	0.0211	BETA
Advanced fibrosis to Compensated cirrhosis	0.0555	0.0111	BETA
Compensated cirrhosis to Compensated cirrhosis with varices	0.0604	0.0121	BETA
Compensated cirrhosis to Decompensated cirrhosis	0.0703	0.0141	BETA
Decompensated cirrhosis to Decompensated cirrhosis with varices	0.1266	0.0253	BETA
Decompensated cirrhosis to transplant	0.0228	0.0046	BETA
Compensated cirrhosis with varices to decompensated cirrhosis with varices	0.0703	0.0141	BETA
Compensated cirrhosis with varices to bleeding	0.1209	0.0242	BETA
Compensated cirrhosis with varices to HCC	0.0264	0.0053	BETA
Decompensated cirrhosis with varices to Bleeding	0.3163	0.0633	BETA
Decompensated cirrhosis with varices to HCC	0.0329	0.0066	BETA
Decompensated cirrhosis with varices to transplant	0.0228	0.0046	BETA

Bleeding to HCC	0.0369	0.0074	BETA
Bleeding to transplant	0.0256	0.0051	BETA
HCC to transplant	0.0408	0.0082	BETA
Asymptomatic liver disease to Death	0.0000	0.0000	BETA
Advanced fibrosis to Death	0.0060	0.0012	BETA
Compensated cirrhosis to Death	0.0219	0.0044	BETA
Decompensated cirrhosis to Death	0.2150	0.0430	BETA
Compensated cirrhosis with varices to Death	0.0219	0.0044	BETA
Decompensated cirrhosis with varices to Death	0.2150	0.0430	BETA
Bleeding to Death	0.2994	0.0599	BETA
HCC_Death	0.5604	0.1121	BETA
Liver transplant to Death	0.1810	0.0362	BETA
Post liver Transplant to Death	0.0435	0.0087	BETA
No CVD to Myocardial infarction	0.0113	0.0023	DIRICHLET
No CVD to Angina	0.0060	0.0012	DIRICHLET
No CVD to Congestive heart failure	0.0026	0.0005	DIRICHLET
No CVD to Stroke	0.0015	0.0003	DIRICHLET
Angina to MI	0.0113	0.0023	DIRICHLET
Angina to CHF	0.0026	0.0005	DIRICHLET
Angina to stroke	0.0015	0.0003	DIRICHLET
Post myocardial infarction to Congestive heart failure	0.0224	0.0045	BETA
Myocardial Infarction to Death	0.0713	0.0143	BETA
Post myocardial infarction to Death	0.0286	0.0057	BETA
Congestive heart failure to Death	0.4300	0.0860	BETA
Stroke to Death	0.0690	0.0138	BETA
Post-stroke to Death	0.2360	0.0472	BETA
No CKD to Microalbuminuria	0.0436	0.0087	DIRICHLET
No CKD to macroalbuminuria	0.0037	0.0007	DIRICHLET
No CKD to end stage renal disease	0.0008	0.0002	DIRICHLET
Microalbuminuria to macroalbuminuria	0.1566	0.0313	DIRICHLET
Microalbuminuria to end stage renal disease	0.0515	0.0103	DIRICHLET
Macroalbuminuria to end stage renal disease	0.4334	0.0867	BETA
End stage renal disease to transplant 18-34	0.1520	0.0230	BETA
End stage renal disease to transplant 35-44	0.1350	0.0200	BETA

End stage renal disease to transplant 45-54	0.1140	0.0170	BETA
End stage renal disease to transplant 55-64	0.0750	0.0110	BETA
End stage renal disease to transplant 65+	0.0390	0.0060	BETA
End stage renal disease to death	0.0884	0.0177	BETA
Macroalbuminuria to death	0.0070	0.0014	BETA
Microalbuminuria to death	0.0004	0.0001	BETA
No CKD to death	0.0000	0.0000	BETA
No retinopathy to Background retinopathy	0.0454	0.0091	DIRICHLET
No retinopathy to Proliferative retinopathy	0.0013	0.0003	DIRICHLET
No retinopathy to Macular Oedema	0.0012	0.0002	DIRICHLET
No retinopathy to Blindness	0.0000	0.0000	DIRICHLET
Background retinopathy to Proliferative retinopathy	0.0595	0.0119	DIRICHLET
Background retinopathy to Macular Oedema	0.0512	0.0102	DIRICHLET
Background retinopathy to Blindness	0.0001	0.0000	DIRICHLET
Proliferative retinopathy to Blindness	0.0038	0.0008	BETA
Macular Oedema to Blindness	0.0016	0.0003	BETA
No Neuropathy to Peripheral Neuropathy	0.0512	0.0102	DIRICHLET
No Neuropathy to Amputation	0.0004	0.0001	DIRICHLET
Peripheral Neuropathy to Amputation	0.0225	0.0045	BETA
Risk of pancreatitis in patients treated with SC alone	[redacted]	[redacted]	BETA
Risk of pancreatitis in patients treated with metreleptin	[redacted]	[redacted]	BETA
Pancreatitis to death	0.2000	0.0400	BETA
Costs and metreleptin dose			
GL Discont. noncompliance - 1 year	1.50%	0.0030	BETA
GL Discont. noncompliance - 2-5 years	1.50%	0.0030	BETA
GL Discont. noncompliance - 10 years+	1.50%	0.0030	BETA
PL Discont. noncompliance - 1 year	3.86%	0.0077	BETA
PL Discont. noncompliance - 2-5 years	3.86%	0.0077	BETA
PL Discont. noncompliance - 10 years+	3.86%	0.0077	BETA
Proportion of patients without dose escalation	26%	0.0522	BETA

Proportion of patients escalating to max dose	13%	0.0260	BETA
Year 1 disease management cost for patients treated with metreleptin	976.38	195.28	GAMMA
Year 2+ disease management costs for patients treated with metreleptin	325.46	65.09	GAMMA
Year 1 disease management costs for patients treated with SC	325.46	65.09	GAMMA
Year 2+ disease management costs for patient treated with SC only	325.46	65.09	GAMMA
Cost of SC medication for GL patient treated with metreleptin	674.17	134.83	GAMMA
Cost of SC medication for GL patients treated with SC alone	2886.00	577.20	GAMMA
Cost of SC medication for PL patient treated with metreleptin	1270.09	254.02	GAMMA
Cost of SC medication for PL patient treated with SC alone	1645.61	329.12	GAMMA
Cost Angina year 1	6854.89	1370.98	GAMMA
Cost Angina year 2+	308.55	61.71	GAMMA
Cost stroke year 1	4461.79	892.36	GAMMA
Cost stroke year 2+	165.87	33.17	GAMMA
Cost congestive heart failure year 1	3847.55	769.51	GAMMA
Cost congestive heart failure year 2+	2779.05	555.81	GAMMA
Cost myocardial infarction year 1	3992.55	798.51	GAMMA
Cost myocardial infarction year 2+	843.24	168.65	GAMMA
Cost microalbuminuria	39.35	7.87	GAMMA
Cost macroalbuminuria	4026.03	805.21	GAMMA
Cost end stage renal disease	5632.97	1126.59	GAMMA
Cost kidney transplant year 1	22043.99	4408.80	GAMMA
Cost kidney transplant year 2+	8233.09	1646.62	GAMMA
Cost asymptomatic liver disease	143.39	28.68	GAMMA
Cost advanced fibrosis	462.28	92.46	GAMMA
Cost compensated cirrhosis	462.28	92.46	GAMMA
Cost decompensated cirrhosis	13901.68	2780.34	GAMMA
Cost compensated cirrhosis with varices	462.28	92.46	GAMMA
Cost decompensated cirrhosis with varices	13901.68	2780.34	GAMMA

Cost bleeding	2839.18	567.84	GAMMA
Cost HCC	13901.68	2780.34	GAMMA
Cost liver transplant year 1	63295.43	12659.09	GAMMA
Cost liver transplant year 2	19659.40	3931.88	GAMMA
Cost Liver transplant year 3+	8984.63	1796.93	GAMMA
Cost pancreatitis episode	1174.11	234.82	GAMMA
Cost background retinopathy	308.42	61.68	GAMMA
Cost proliferative retinopathy	1050.49	210.10	GAMMA
Cost macular oedema	3059.64	611.93	GAMMA
Cost blindness year 1	5974.42	1194.88	GAMMA
Cost blindness year 2+	5772.24	1154.45	GAMMA
Cost neuropathy	386.81	77.36	GAMMA
Cost amputation year 1	6090.60	1218.12	GAMMA
Cost amputation year 2+	0.00	0	GAMMA
Health state utility decrements			
Decrement angina	-0.09	0.0180	BETA
Decrement stroke	-0.16	0.0328	BETA
Decrement congestive heart failure	-0.11	0.0216	BETA
Decrement myocardial infarction	-0.06	0.0110	BETA
Decrement microalbuminuria	0.00	0.0000	BETA
Decrement macroalbuminuria	-0.05	0.0220	BETA
Decrement end stage renal disease	-0.22	0.0690	BETA
Decrement kidney transplant year 1	-0.15	0.0700	BETA
Decrement kidney transplant year 2+	-0.08	0.0230	BETA
Decrement asymptomatic liver disease	-0.03	0.0060	BETA
Decrement advanced fibrosis	-0.15	0.0300	BETA
Decrement compensated cirrhosis	-0.27	0.0540	BETA
Decrement decompensated cirrhosis	-0.33	0.0660	BETA
Decrement compensated cirrhosis with varices	-0.27	0.0540	BETA
Decrement decompensated cirrhosis with varices	-0.33	0.0660	BETA
Decrement bleeding	-0.33	0.0660	BETA
Decrement hepatocellular carcinoma	-0.33	0.0660	BETA
Decrement liver transpant year 1	-0.07	0.0140	BETA
Decrement liver transplant year 2+	-0.02	0.0040	BETA
Decrement pancreatitis	-0.13	0.0260	BETA
Decrement background retinopathy	-0.03	0.0054	BETA

Decrement proliferative retinopathy	-0.07	0.0140	BETA
Decrement macular oedema	-0.04	0.0080	BETA
Decrement blindness	-0.07	0.0148	BETA
Decrement neuropathy	-0.08	0.0168	BETA
Decrement amputation	-0.28	0.0560	BETA
Utility <18	0.93	0.1858	BETA
Utility 18-24	0.93	0.1858	BETA
Utility 25-34	0.92	0.1838	BETA
Utility 35-44	0.89	0.1786	BETA
Utility 45-54	0.86	0.1710	BETA
Utility 55-64	0.81	0.1620	BETA
Utility 65-74	0.77	0.1546	BETA
Utility 75+	0.70	0.1406	BETA

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

Metreleptin for treating lipodystrophy [ID861]

Re-submission

May 2020

File name	Version	Contains confidential information	Date
		Yes	

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature Searching

A1. *Please confirm the host for the Embase, Medline and Medline in Process searches, 'EMBASE interface' is not a recognised host.*

'EMBASE interface' refers to https://www.embase.com/#search.

A2. *Please confirm the host for the CENTRAL search, Table 59 states the 'Cochrane Library Interface' but the search syntax does not seem to correspond to that.*

'Cochrane Library Interface' refers to the advanced search function at https://www.cochranelibrary.com/advanced-search.

A3. *The search strategy provided in Table 63 Appendix 3 is incomplete, it only contains lines 13-17, please provide the full search strategy.*

Combined searches were performed for clinical, economic evaluations, utility, and cost and resource use studies. The full EMBASE, Medline, Medline (R) In-Process search strategy (EMBASE interface) is detailed in Table 1. Index 16 in the search strategy combines the population search strategy with the filters to identify economic evaluations, utility, and cost and resource use studies. Index 17 combines the search and filter combination from index 16

(economic evaluations, utility, and cost and resource use studies) and index 12 (clinical studies).

Table 1: Full EMBASE Systematic literature review search strategy

Clinical studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Population	('lipodystrophy'/exp OR lipodystrop* OR 'lipid dystroph*' OR lipoatroph*) AND (familial OR inherited OR genetic OR congenital OR partial OR acquired OR generalised OR generalized OR 'fpld*' OR 'cgl*' OR 'agl*' OR 'apl*' OR 'dunnigan adj syndrom*' OR 'lawrence adj syndrom*' OR 'berardinelli* adj syndrom*' OR 'barraquer* adj syndrom*' OR 'wiedemann adj rautenstrauch' OR 'donohue adj syndrom*' OR kobberling OR koebberling OR 'diabetes mellitus'/exp OR 'severe' OR 'insulin resistance'/exp OR 'leptin deficiency'/exp)	7,797
2	Intervention	metreleptin OR myalept* OR leptin	58,159
3	Comparators (Diet and exercise)	'Exercise'/de OR 'Physical Education'/de and 'Training'/de OR 'Physical Fitness'/de OR 'Life Style'/de OR 'Health Education'/de OR 'Health Behavior'/de OR 'Health Promotion'/de OR 'Sports'/de OR 'Physical Exertion'/de OR 'Exercise Therapy'/de OR 'Nutrition Therapy'/de OR 'Diet Therapy'/de OR 'Feeding Behavior'/de OR 'Running'/de OR 'Diabetic diet'/de OR 'Jogging'/de OR 'Swimming'/de OR 'Walking'/de OR 'Bicycling'/de OR exercise:ab,ti OR exercising:ab,ti OR exertion*:ab,ti OR sport:ab,ti OR sports:ab,ti OR walking:ab,ti OR jogging:ab,ti OR swimming:ab,ti OR 'strength train*':ab,ti OR 'resistance train*':ab,ti OR 'aerobic train*':ab,ti OR 'physical education*':ab,ti OR 'physical fitness':ab,ti OR nutrition:ab,ti OR nutritional:ab,ti OR 'life style':ab,ti OR lifestyle:ab,ti OR 'health behav*':ab,ti OR 'health educ*':ab,ti OR 'health promot*':ab,ti OR 'physical activit*':ab,ti OR bicycling:ab,ti OR 'weight lift*':ab,ti OR running:ab,ti OR gymnastic*:ab,ti OR dance:ab,ti OR dancing:ab,ti OR diet:ab,ti	1,845,901
4	Comparators (for abnormal physical appearance)	'esthetic surgery'/de OR 'cosmetic surgery':ab,ti OR 'cosmetic techniques':ab,ti OR 'esthetic surgery':ab,ti OR 'surgery, cosmetic':ab,ti OR 'surgery, esthetic':ab,ti	15,487
5	Comparators (for hyerphagia)	'anorexigenic agent'/de OR 'agent, anorexiant':ab,ti OR 'anorectic agent':ab,ti OR 'anorectic drug':ab,ti OR 'anorexant agent':ab,ti OR 'anorexiant':ab,ti OR 'anorexiant agent':ab,ti OR 'anorexiant drug':ab,ti OR 'anorexiants':ab,ti OR 'anorexic agent':ab,ti OR 'anorexic drug':ab,ti OR 'anorexigen':ab,ti OR 'anorexigenic agent':ab,ti OR 'anorexigenic compound':ab,ti OR 'anorexigenic drug':ab,ti OR 'antiappetite agent':ab,ti OR 'appetite depressant	34,519

		agent':ab,ti OR 'appetite depressants':ab,ti OR 'appetite inhibitor':ab,ti OR 'appetite reducer':ab,ti OR 'appetite reducing drug':ab,ti OR 'appetite restrainer':ab,ti OR 'appetite suppressant':ab,ti OR 'appetite suppressing agent':ab,ti OR 'bariatric surgery'/de	
6	Comparators (for insulin resistance and/or diabetes)	'2,4 thiazolidinedione derivative'/de OR '2,4 thiazolidinedione derivative':ab,ti OR 'thiazolidine 2, 4 dione derivative':ab,ti OR 'thiazolidinedione':ab,ti OR 'thiazolidinedione derivative':ab,ti OR thiazolidinediones:ab,ti OR 'metformin'/de OR 'dipeptidyl peptidase iv inhibitor'/de OR 'dpp 4 inhibitor':ab,ti OR 'dpp iv inhibitor':ab,ti OR 'dipeptidyl peptidase 4 inhibitor':ab,ti OR 'dipeptidyl peptidase iv inhibitor':ab,ti OR 'dipeptidyl peptidase iv inhibitors':ab,ti OR 'dipeptidyl-peptidase iv inhibitors':ab,ti OR 'dipeptidylpeptidase 4 inhibitor':ab,ti OR 'dipeptidylpeptidase iv inhibitor':ab,ti OR 'gliptin':ab,ti OR 'gliptins':ab,ti OR 'glucagon like peptide 1 receptor agonist'/de OR 'glp 1 agonist':ab,ti OR 'glp 1 receptor agonist':ab,ti OR 'glucagon like peptide 1 agonist':ab,ti OR 'glucagon like peptide 1 receptor agonist':ab,ti OR 'glucagon like peptide 1 receptor stimulating agent':ab,ti OR 'long acting glp 1 agonist':ab,ti OR 'long acting glp 1 receptor agonist':ab,ti OR 'long acting glucagon like peptide 1 agonist':ab,ti OR 'long acting glucagon like peptide 1 receptor agonist':ab,ti OR 'sodium glucose cotransporter 2 inhibitor'/de OR 'sglt2 inhibitor':ab,ti OR 'sglt2 inhibitors':ab,ti OR 'gliflozin':ab,ti OR 'gliflozin derivative':ab,ti OR 'gliflozins':ab,ti OR 'sodium dependent glucose cotransporter 2 inhibitor':ab,ti OR 'sodium glucose co-transporter 2 inhibitor':ab,ti OR 'sodium glucose cotransporter 2 inhibitor':ab,ti OR 'sodium-glucose transporter 2 inhibitors':ab,ti OR 'insulin'/de OR 'sulfonylurea'/de OR 'sulfonurea':ab,ti OR 'sulfonyl urea':ab,ti OR 'sulfonylcarbamide':ab,ti OR 'sulfonylurea':ab,ti OR 'sulphonurea':ab,ti OR 'sulphonylurea':ab,ti	397,147
7	Comparators (for HTG)	'hydroxymethylglutaryl coenzyme a reductase inhibitor'/de OR ('hmg coa reductase inhibitor':ab,ti OR 'hmg coa reductase inhibitors':ab,ti OR 'hmg coenzyme a reductase inhibitor':ab,ti OR 'hmg-coa reductase inhibitors':ab,ti OR 'hydroxymethylglutaryl coa reductase inhibitors':ab,ti OR 'hydroxymethylglutaryl coenzyme a reductase inhibitor':ab,ti OR 'hydroxymethylglutaryl-coa reductase inhibitors':ab,ti OR statin:ab,ti) AND drug:ab,ti OR 'statins':ab,ti OR 'vastatin':ab,ti OR 'fibric acid derivative'/de OR 'fibrate':ab,ti OR 'fibrate derivative':ab,ti OR 'fibrates':ab,ti OR 'fibric acid':ab,ti OR 'fibric acid derivative':ab,ti OR 'fibric acid derivatives':ab,ti OR 'fibric acids':ab,ti OR ‘fish oil’/de OR 'plasma exchange system'/de OR 'plasma exchange device':ab,ti OR 'plasma exchange system':ab,ti	72,963

8	Comparators (for fatty liver disease)	'cholic acid'/de OR '3, 7, 12 trihydroxycholanic acid':ab,ti OR '3alpha, 7 alpha, 12alpha trihydroxy 5beta cholanic acid':ab,ti OR '3alpha, 7alpha, 12alpha trihydroxy 5beta cholanic acid':ab,ti OR 'chenocholic acid':ab,ti OR 'chobile':ab,ti OR 'cholalic acid':ab,ti OR 'cholate':ab,ti OR 'cholate sodium':ab,ti OR 'cholbam':ab,ti OR 'cholic acid':ab,ti OR 'cholic acid sodium salt':ab,ti OR 'felagol':ab,ti OR 'hydrocholate sodium':ab,ti OR 'kolbam':ab,ti OR 'lipiodol cholic acid salt':ab,ti OR 'nsc 6135':ab,ti OR 'nsc6135':ab,ti OR 'orphacol':ab,ti OR 'sodium cholate':ab,ti OR 'trihydroxycholanic acid':ab,ti OR 'trihydroxycholanoic acid':ab,ti OR 'trihydroxycholic acid':ab,ti	9,693
9	Study types: RCT Filter (https://www.sign.ac.uk/search-filters.html)	('Clinical Trial'/de OR 'Randomized Controlled Trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR Randomization/exp OR 'Single Blind Procedure'/de OR 'Double Blind Procedure'/de OR 'Crossover Procedure'/de OR 'PLACEBO'/de OR 'randomi#ed controlled trial*':ab,ti OR 'rct':ab,ti OR (random* NEXT/2 allocat*):ab,ti OR 'single blind*':ab,ti OR 'double blind*':ab,ti OR ((treble OR triple) NEXT/1 blind*):ab,ti OR 'placebo*':ab,ti OR 'Prospective Study'/de)	2,153,377
10	Observational studies filter (https://www.sign.ac.uk/search-filters.html)	('clinical study'/de OR 'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study or studies)):ti,ab OR ('case control' NEXT/1 (study or studies)):ti,ab OR ('follow up' NEXT/1 (study or studies)):ti,ab OR (observational NEXT/1 (study or studies)):ti,ab OR (epidemiologic* NEXT/1 (study or studies)):ti,ab OR ('cross sectional' NEXT/1 (study or studies)):ti,ab)	3,309,096

11	ERG filter (https://njl-admin.nihr.ac.uk/document/download/20211010)	'incidence' OR 'standardized incidence ratio' OR 'Prevalence' OR 'standardized mortality ratio' OR 'demography' OR 'epidemiological data' OR 'mortality' OR 'disease progression' OR 'disease activity' OR 'morbidity' OR occurrence*:ti,ab,kw OR incidence*:ti,ab,kw OR prevalence*:ti,ab,kw OR episode*:ti,ab,kw OR mortalit*:ti,ab,kw OR morbidit*:ti,ab,kw OR epidemiolog*:ti,ab,kw OR demograph*:ti,ab,kw OR ((natural NEXT/2 history):ti,ab,kw) OR ((disease NEXT/2 progres*):ti,ab,kw) OR ((disease NEXT/2 course):ti,ab,kw) AND [14-10-2009]/sd	2,935,364
12	Combine terms	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) AND (#9 OR #10) OR (#1 AND #11)	1,580

Economic evaluations, utility, and cost and resource use studies search strategy

Index	Description	Search terms	Hits
13	Economic Filter (https://www.sign.ac.uk/search-filters.html)	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost* AND [6-3-2017]/sd	137,293
14	Health state utility values filter (http://www.yhec.co.uk/yhec-content/uploads/2015/06/Poster-374-Sensitivity-Of-A-Search-Filter.pdf)	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq	211,987

		OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti AND [6-3-2017]/sd	
15	Resource use filter	(burden OR resource*):ti OR (burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti OR (resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti OR 'office visits':ab,ti OR 'ambulatory care'/de OR (visit OR visits OR visited):ab,ti OR appointment*:ab,ti OR hospitalization/de OR (hospitalization* OR hospitalisation* OR hospitalised OR hospitalized):ab,ti OR (admission* OR readmission* OR admitted OR readmitted):ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR (bed NEXT/3 day*):ab,ti OR ((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti OR ((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti OR ((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti AND [6-3-2017]/sd	378,687
16	Combine terms	#1 AND (#13 OR #14 OR #15)	122
17	Combine terms	#12 OR #16	1,605

A4. *Table 64 Appendix 3 contains the results of a CENTRAL search run in the Cochrane library and not the CRD searches of the HTA and NHS EED databases. Please provide the full search strategies of these resources.*

The full Centre for Reviews and Dissemination (CRD) Health Technology Assessment (HTA) and National Health Service (NHS) Economic Evaluation Database (EED) search strategy is detailed in Table 2.

Table 2: CRD HTA and NHS EED Search Strategy (via University of York website)

Economic evaluations, utility and dis-utility, and cost and resource use studies search strategy			
Index	**Description**	**Search terms**	**Hits**

1	Terms for population	lipodystrop OR "lipid dystroph" OR lipoatrophy OR dunnigan OR "lawrence syndrom" OR berardinelli OR barraquer OR wiedemann OR rautenstrauch OR donohue OR kobberling OR koebberling OR leptin	46
2	Economic filter	economics OR cost OR burden OR econ* OR "health care cost" OR "indirect cost" OR productivity	21,560
3	QoL filter	qol OR "quality of life" OR "patient satisfaction" OR utility OR "patient reported outcome" OR "time tradeoff" OR TTO OR "activities of daily living" OR ADL OR "social impact"	11,543
4	Combine population, filters and date limit	#1 AND (#2 OR #3) from 2017 to 2019	0

A5. *Pease provide the EuroQol database search strategy.*

The full EuroQol database search strategy is detailed in Table 3.

Table 3: EuroQol database search strategy

Economic evaluations, utility and dis-utility, and cost and resource use studies search strategy			
Index	**Description**	**Search terms**	**Hits**
1	Terms for population	‘lipodystrop’ OR ‘lipid dystroph’ OR ‘lipoatrophy’ OR 'dunnigan' OR 'lawrence syndrom' OR 'berardinelli' OR ‘barraquer’ OR 'wiedemann’ OR ‘rautenstrauch' OR 'donohue' OR ‘kobberling’ OR ‘koebberling’ OR ‘leptin’	0
2	Combine and date limits	#1 from 2017 to 2019	0

A6. *Please advise if the Econlit database was searched, and if so, provide the strategy.*

The Econlit database was not searched as it is not considered a core database to be searched according to NICE guidelines or in the University of York Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care (1,2).

Decision problem

A7. Priority question: *In the statement of the decision problem the company state that the comparator should be 'Supportive care', rather than 'Established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes).' They also state that 'Diet lifestyle modifications are a mainstay of disease management irrespective of treatment…'. Also, on page 17 of the submission the company state 'Lipodystrophy is currently primarily managed through diet and lifestyle modification'. Finally, on page 196 it states: 'Hence, the introduction of metreleptin is not expected to involve any significant additional service infrastructure.'*

a) *Can the company confirm that the level and nature of diet and lifestyle modification, lipid lowering drugs and medications for diabetes was the same for the metreleptin studies as it was for the Natural History study. If not, then can the company point to where these differences are itemised or, alternatively provide such information.*
b) *Can the company confirm the expected level and nature of diet and lifestyle modification, lipid lowering drugs and medications for diabetes with metreleptin in clinical practice.*
c) *Can the company confirm that the level and nature of diet and lifestyle modification, lipid lowering drugs and medications for diabetes in the economic model is consistent with the evidence i.e. for the intervention, as observed in the metreleptin studies, and, for the comparator, as in the Natural History study. If this is not the case then can the company provide adequate justification.*

a) The study design of the National Institute of Health (NIH) studies 991265/20010769 and the GL/PL Natural History study have some specific differences that must be considered when making such a comparison.

Lipodystrophy initiated metreleptin treatment at the NIH over a long period of time, during which clinical understanding of lipodystrophy was rapidly evolving (3). Patients were selected to participate in the trials based on the presence of generalised or partial lipodystrophy, as well as one or more metabolic complications of lipodystrophy, including insulin resistance, diabetes, or hypertriglyceridaemia. In many (but not all) cases, these patients had significant

experience with traditional treatments for high triglycerides and high HbA1c and these treatments were insufficient to control their disease. In many cases children were treated prior to the onset of severe metabolic disease, with the goal of preventing the development of uncontrolled diabetes, hypertriglyceridaemia, and pancreatitis.

Diet and lifestyle modification

In the methodology of the NIH studies 991265/20010769 no specific diet was defined for the patients, nor was dietary compliance and caloric intake recorded.

Lipodystrophies are characterised by partial or complete absence of adipose tissue which can lead to leptin deficiency (4). Leptin is a hormone that acts at the level of the central nervous system (hypothalamus), regulating appetite, inhibiting food intake and is responsible for generating the signal of satiety in the brain. People who are leptin deficient do not have this mechanism of satiety and brake of the caloric ingestion, showing an insatiable hunger. For this reason, current clinical practice guidelines consider diet as one of the fundamental pillars in the therapy of the metabolic complications of lipodystrophy (5). Studies of specific diets in lipodystrophy are still lacking however, and recommendations rely on sparse literature and clinical experience. Alternatively, there is compelling evidence in the literature that there is no “one size fits all” eating plan evident for the management of “regular” diabetes mellitus and that nutrition therapy recommendations need to be adjusted regularly based on changes in an individual’s life circumstances, preferences, and disease course (6). Treatment with metreleptin in lipodystrophy patients improves eating behaviour by increasing satiety and reducing hunger. Recent long-term (>150 weeks) results of metreleptin show a sustained effect on eating behaviour with an increase in satiety as well as a reduction in hunger (7). By correcting hyperphagia with metreleptin treatment, patients are able to adhere to a healthy diet, which provides an added metabolic benefit. It should be noted that in patients under conditions of strict dietary control and hospitalisation, metreleptin improves metabolic disease far beyond what the diet alone could achieve (3). In addition, metreleptin is known to improve insulin sensitivity and lower circulating and hepatic triglyceride levels, regardless of food intake (8).

According to the approved label in Europe, metreleptin is indicated, together with diet, as a replacement treatment to treat the complications derived from a leptin deficit in lipodystrophy patients. Although metreleptin has shown that its metabolic effects are independent of diet, reducing food intake also helps to improve patients' metabolic profile. Without brain-level control of hunger and satiety, following a diet in lipodystrophy patients is virtually impossible.

Lipid lowering drugs and medications for diabetes

In NIH studies 991265/20010769, as noted in Section 9.4.7 (Prior and Concomitant Therapy), patients were advised by their doctors as to which permitted concomitant medications were necessary to take in addition to metreleptin. At baseline, the level and nature of concomitant medications, including lipid lowering drugs and medications for diabetes can be found for each study in the relevant CSR or technical report:

- NIH studies 991265/20010769 – Table 12 of the CSR (9)
- NIH follow-up study – Tables 2 and 6 of the technical report (10)

Results in the controlled concomitant medication full analysis set of the PL subgroup 1 were very similar to those in the full analysis set, with an actual decrease in HbA1c of 0.7%, from 8.2% at baseline to 7.6% at month 12/LOCF ($p = 0.008$). Mean (median) TG concentrations in the controlled concomitant medication full analysis set were reduced by 34%, from 12.6 (5.7) mmol/L at baseline to 5.4 (3.9) mmol/L at month 12/LOCF ($p < 0.001$) (9). Similar significant and clinically meaningful results were obtained in the controlled concomitant medication full analysis set of the GL population (from 8.5 to 6.6% [$p < 0.001$] for HbA1c; from 8.6 to 3.2 mmol/L [$p = 0.026$] for TGs) (11). The similarity of the efficacy results between the full analysis and controlled concomitant medication full analysis set populations indicated that the results were only minimally influenced by any increases in, or additions to, background medication, but rather were due to treatment with metreleptin.

As described in responses to A20, A21 and in the CS (section 9.8.1), the GL/PL Natural History study was based on international chart reviews, including patients from Brazil, Turkey and the US, and captures data across the entire time period for which data were available within each patient’s medical chart; the observation period spanned from birth until loss to follow-up, death, or date of chart abstraction, whichever occurred first, the mean duration of

follow-up was 7.6 years in the overall cohort (12). This study aimed to describe the natural history of metreleptin-naïve patients with non-HIV-related GL and PL based on a range of lipodystrophy disease attributes, including organ abnormalities, disease progression, and mortality. The potential impact of any symptomatic treatment on these attributes was not investigated in this study and therefore, medication use was only reported during the baseline period which spanned between birth and the first known date of GL or PL diagnosis, shown in Table 4 (13).

Table 4: GL/PL Natural History study: baseline medication use

	GL and PL	GL	PL
Total number of patients	230	81	149
Baseline information available, n (%)	89 (38.7)	30 (37.0)	59 (39.6)
Any baseline medication use, n (%)	45 (50.6)	10 (33.3)	35 (59.3)
Any fibrates, n (%)	19 (21.3)	5 (16.7)	14 (23.7)
Any statin, n (%)	8 (9.0)	1 (3.3)	7 (11.9)
Any insulin, n (%)	19 (21.3)	6 (20.0)	13 (22.0)
Any oral antidiabetic agent, n (%)	34 (38.2)	6 (20.0)	28 (47.5)
Abbreviations: GL, Generalised lipodystrophy; PL, Partial lipodystrophy. Source: Adapted from GL/PL Natural History Technical Report, Appendix B (13)			

In the previous FED (section 4.3), it was noted that "*clinical experts confirmed that the trial populations were generalisable to patients seen in clinical practice in England*" (14). After further consultation on this with clinical experts (Addenbrooke's Hospital), they continue to uphold that the trial population in the NIH studies 991265/20010769 is generalisable to UK clinical practice.

Although the lipodystrophy treatment guideline provides some guidance regarding symptomatic treatment options for the metabolic derangements such as metformin and statins, the supportive therapy has 1) its limitations and 2) has to be adjusted regularly based on changes in an individual's life circumstances, the metabolic situation, and the disease course (5). There is also an impact of the leptin replacement therapy with metreleptin on the

use of supportive therapy. Many patients were able to discontinue their use of insulin, antidiabetic medications, or lipid-lowering medications in the clinical trials.

As highlighted in the statement of the European Consortium of Lipodystrophies, most forms of lipodystrophy are very difficult to treat. A hypertriglyceridaemia far above 500 mg/dL is not uncommon in these patients, nor is an insulin requirement with significantly more than 200 units of insulin per day. With the currently available symptomatic drugs, the severe metabolic disorders caused by leptin deficiency and lack of fat storage capacity are difficult to control. Metreleptin is the first specific, cause-related therapy for these diseases (15).

b) In clinical practice, the level and nature of lipid lowering drugs and antidiabetic medications with metreleptin are based on that observed in the NIH studies 991265/20010769. These NIH studies classified supportive care medication as follows:

- Insulin (assumed to be intermediate or long acting insulin, combined with fast acting insulin in a 70:30 ratio)
- Oral antidiabetic medication: biguanides, thiazolidinediones and sulfonylureas
- Lipid lowering therapies: HMG CoA reductase inhibitors and other lipid modifying agents
- Other concomitant medications: lisinopril and enalapril.

The strength of the most commonly prescribed medication was assumed to be the daily dose (within the dose recommended in the British National Formulary [BNF]).

After further consultation with clinical experts (Addenbrooke's Hospital), they continue to uphold that the concomitant medications, observed at baseline and during the NIH studies 991265/20010769, are generalisable to UK clinical practice.

The Delphi Panel (consisting of 10 international clinical experts, including 3 from the UK, reached consensus on the proportion of lipodystrophy patients being treated with metreleptin that discontinue supportive care medications or reduce the dose of supportive care (SC) medications (16). This is consistent with the published data from NIH studies 991265/20010769 (8).

c) The comparator for the analysis is SC, which comprises the use of conventional anti-hyperglycaemic and lipid lowering medications currently used to manage metabolic complications associated with lipodystrophy. This is consistent with the scope. Diet and lifestyle modifications are, with the described limitations caused by the leptin deficiency, exercise restrictions in lipodystrophy patients with cardiomyopathy, and/or by the type of lipodystrophy, a mainstay of disease management irrespective of treatment, and therefore is considered distinct from SC.

The intervention for the analysis is metreleptin, which is the first and only approved therapy for the treatment of lipodystrophy, that addresses the underlying cause of the disease, the leptin deficiency.

For the cost-effectiveness model, as described in Section 12.3.6 of the CS, the costs in the SC alone arm were calculated based on the SC medications used by patients in the NIH studies 991265/20010769 at baseline (see Appendix 13, Table 121 in the company submission (CS)), and applying this to relevant NHS prescription cost data, BNF and NHS drug tariffs.

The Delphi Panel reached consensus on the proportion of lipodystrophy patients being treated with metreleptin that discontinue SC medications or reduce the dose of SC medication. Therefore, the SC alone costs for patients on metreleptin has been adjusted in the model to reflect the reductions they specified (see Appendix 13, Table 128 and Table 129 in the CS for further detail).

Clinical trials

A8. *Section 6.2 (CS, page 47) states: 'There is limited published data available on the incidence and prevalence of lipodystrophy in England. However, there are relevant and accurate estimates available based on Early Access Programme (EAP) data from a decade of metreleptin use in UK clinical practice at Addenbrooke's. [redacted] lipodystrophy patients are currently receiving metreleptin at Addenbrooke's under the EAP – [redacted] and [redacted] patients with GL and PL, respectively. 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] for GL and [redacted] for PL).' Table 54 (Section 13.1, page 228 of the CS) provides an summary of the estimated numbers of patients with PL and GL who would be eligible for treatment with metreleptin in years 1 through 5, leading to a total number of 40 in year 5.

a) *Please explain why only [redacted] patients with PL were added to the total in year two and only [redacted] patients with PL were added in year 4.*
b) *Please also provide supporting evidence for the estimate of [redacted] new patients per year. How many patients, with PL and GL, have joined the Addenbrooke's EAP each year, since its inception (including patients who have subsequently left the programme)?*

a) The data provided in Table 54 of the CS includes the adjustments for metreleptin uptake rate and discontinuation due to non-compliance and stopping rules.

Lipodystrophy patient numbers were based on EAP data from Addenbrooke's in 2020. The clinical experts at Addenbrooke's estimated that [redacted] additional patients per year would be diagnosed with GL and [redacted] new patients each year would be diagnosed with PL (so [redacted] new patients each year). In the previous submission (section 13.1), mortality was assumed based on [redacted] patient with PL dying each year and [redacted] patient with GL dying every 2 years, so these were combined with the uptake. For consistency, Amryt would like to update the projected patient numbers for metreleptin to adjust for mortality ([redacted] patient every [redacted] years for GL and [redacted] patient every year for PL), as shown in Table 5.

Table 5: Projected patient numbers likely to recieve metreleptin from 2020 Addenbrooke's data

	Year 1* (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)
GL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GL, Generalised lipodystrophy; PL, Partial lipodystrophy * Based on Addenbrooke's EAP data in 2020					

After adjustment for the estimated uptake rate (now assumed to be 85% in Year 2 rising to 90% in year 5 for new patients) and discontinuation from Year 2 (non-compliance from NIH studies 991265/200110769 [1.50% for patients with GL and 3.86% for patients with PL] and stopping rules [0% for patients with GL and 4.54% for patients with PL]), the number of patients expected to be treated with metreleptin are listed in Table 6.

Table 6: Estimated patient numbers on treatment with metreleptin (adjusted for uptake rate, non-compliance and stopping rules)

	Year 1 (2020)	**Year 2 (2021)**	**Year 3 (2022)**	**Year 4 (2023)**	**Year 5 (2024)**
GL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GL, Generalised lipodystrophy; PL, Partial lipodystrophy					

b) The estimate of [redacted] new patients per year ([redacted] additional patients per year would be diagnosed with GL and [redacted] new patients each year would be diagnosed with PL (see Table 5)) was provided by two clinical experts at Addenbrooke's Hospital, where the Early Access Programme (EAP) is run. Their estimates were based on previous years' activity. Each year, since 2002, the number of patients joining the EAP and leaving the EAP (due to discontinuation or death) is shown in Table 7.

Table 7: Number of patients joining and leaving the Addenbrooke's EAP

Year	**Number of patients joining the Addenbrooke's EAP (n)**		**Number of patients leaving the Addenbrooke's EAP (n)**	
	GL	**PL**	**GL**	**PL**

2002	1	-	-	-
2003	1	-	-	-
2004	-	-	-	-
2005	-	-	-	-
2006	-	-	-	-
2007	-	1	-	-
2008	1	2	-	-
2009	-	2	-	-
2010	-	1	-	1
2011	-	1	-	-
2012	4	3	-	-
2013	-	-	-	-
2014	2	2	-	-
2015	-	3	-	1
2016	1	-	-	1
2017	-	5	1	2
2018	-	-	1	2
2019	-	1	-	1
Abbreviations: GL, Generalised lipodystrophy; PL, Partial lipodystrophy				

A9. *Please provide copies of any protocols, reports or other data sources relating to the ongoing studies, referred to in Section (CS, pages 32 to 33). In particular, please provide any data on patient-perceived outcomes listed in Section 1 (CS, page 26), e.g. need for ongoing antidiabetic and lipid lowering treatment, incidence of complications of diabetes and of organ damage, for patients currently being treated under the Addenbrooke's EAP as well any patients who have discontinued treatment.*

QuaLip and Addenbrooke's data collection reports have been provided in the accompanying reference pack (17,18). Analyses are currently being undertaken by ECLip using data from the ECLip lipodystrophy (LD) Disease Registry, but at time of submission no reports have been published (19).

The NIH Follow Up study captured also data on other lipodystrophy symptoms, including liver abnormality (94%), hyperphagia (79%), impaired physical appearance (77%), elevated protein excretion (75%), kidney abnormality (63%), hypertension (58%), elevated liver enzymes (50%), and reproductive dysfunction (80% of females of reproductive age). In order to quantify the quality of life consequences, a discrete choice experiment was completed, and the resulting utility decrements were used to estimate the quality adjusted life-year (QALY) consequences of changes in lipodystrophy attribute prevalence before and after metreleptin treatment initiation. A dramatic reduction in the prevalence of acute pancreatitis events was observed following metreleptin treatment. Large reductions in prevalence following treatment also occurred for hyperphagia, ability to work/attend school, elevated TG levels, impaired physical appearance, and hyperglycaemia (20).

A10. *Section 9.3.1 (CS, page 81) describes the results of the SLR and states that: 'There were 38 observational references which evaluated metreleptin as an intervention, covering 12 clinical studies, 35 observational references which did not include metreleptin as an intervention, and one randomised controlled trial (RCT) which compared Cholic Acid therapy with placebo. There were no references identified which compared metreleptin to standard of care alone.' Tables 68 to 79 (CS, section 17.6.1) list 19 publications, in relation to 12 studies, about metreleptin and Table 80 (CS, section 17.6.1) lists a further 20 publications on metreleptin with no associated study number. Tables 81 to 84 (CS, section 17.6.1) list a total of 34 non-metreleptin publications.*

Since all of these publications are listed as meeting the inclusion criteria specified in Section 17.5.1 (CS, Table 67, pages 286 to 287), please explain why only results from selected publications relating to NIH studies 991265/20010769, the NIH follow-up study, study FHA101 and the GL/PL Natural History study are reported.

The detailed discussion in Section 9 on these studies focuses on the main studies considered during the European Medicines Agency (EMA) regulatory review of metreleptin and / or relevant for the indirect treatment comparison. However, all studies identified in the systematic literature review are explained in more detail in Appendix 6 of the company submission. Further details of the studies are explained below.

In the systematic literature review for clinical studies, there were 12 clinical studies where metreleptin was included as an intervention and with a study code specified (see tables 68 to

79 in company submission) – this included 10 single arm studies (two of which are the pivotal NIH studies 991265 and 2001076) , one that is assumed to be a single arm study (the publication is an abstract with insufficient relevant data) (21), and the remaining NCT01778556 study includes one paper reporting two treatment arms (cross-over study of only 21 days) (22). The remaining references in table 80 of the company submission were either abstracts (with insufficient data reported) or single arm studies. Pair-wise meta-analyses are not feasible for single arm studies.

The 35 non-metreleptin publications were observational studies (except one was a randomised controlled trial) and mostly contained insufficient data (17 of the publications were abstracts), while the remaining had relatively small sample sizes in each study.

When considering the approach for an indirect treatment comparison, due to the lack of head-to-head data between metreleptin and supportive care, it was identified that the use of individual patient level (IPD) data to conduct such an analysis was ideal. Using IPD permitted a means by which to adjust for differences in baseline population characteristics when generating clinical effectiveness estimates between an intervention and comparator where only single arm data is available. A traditional Bayesian indirect treatment comparison was not considered relevant because it requires links to be formed between the intervention and comparator via multiple studies (the main metreleptin studies are single arm) and sufficiently homogenous populations across the studies included.

NIH studies 991265/20010769 and the NIH follow-up study were deemed most relevant as they are by far the longest and largest trials ever conducted within lipodystrophy, and thus comprise of the most robust and thorough source of metreleptin individual patient-level data (IPD). As highlighted by section 4.3 of the Final Evaluation Document (FED), "*clinical experts confirmed that the trial populations [NIH studies 991265/20010769] were generalisable to patients seen in clinical practice in England*" (14). In addition, NIH studies 991265/20010769, combined with study FHA101 are considered the main clinical trials by the EMA in their assessment of metreleptin (23). The GL/PL Natural History study was identified through the clinical SLR as highly relevant because it comprises the largest cohort of lipodystrophy patients who have never received leptin as the only available lipodystrophy-specific therapy (a crucial characteristic for the purpose of our intended comparison) for which IPD is available to us. Only one other Natural History study was identified in the systematic literature review

(24), however this study comprised of 33 CGL patients, which would be inappropriate for the ITC because only one lipodystrophy type was considered. Comparatively, the GL/PL Natural History study contains 230 GL and PL patients (12). The GL/PL Natural History study was therefore the most appropriate SC arm for the indirect treatment comparison analysis in Section C of the CS.

As such, we only reported results in the main body of the submission from publications relating to NIH studies 991265/20010769, the NIH follow-up study, study FHA101 and the GL/PL Natural History study due to their relevance in the clinical effectiveness of metreleptin.

A11. Priority Question: Please provide full CSRs (including all appendices and statistical analysis plans) for all key studies used in the clinical effectiveness or cost effectiveness sections of the CS:

a) NIH 991265/20010769 (NCT00025883). Open-label, single-arm study conducted at the NIH in the US.
b) NIH follow-up study
c) 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.
d) GL/PL Natural History study.

The requested documents are included as zipped folders as part of the reference pack for this set of responses to ERG questions.

A12. Priority Question: Table A1 under the heading 'Rationale for variation from scope' (in line with regulatory approval) indicates that the relevant GL population is adults and children over 2 years of age and the relevant PL population is adults and children 12 years of age, when standard treatments have failed. The CS defines a PL subgroup: 'patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L.'

a) *Is the PL subgroup being treated as representing patients for whom standard treatments have failed? If yes, please provide supporting information.*
b) *Please provide the number of GL patients in each of the key studies (NIH 991265/20010769, NIH follow-up study, FHA101 and GL/PL Natural History study) who were under two years of age.*

c) *Please provide the number of PL patients in each of the key studies (NIH 991265/20010769, NIH follow-up study, FHA101 and GL/PL Natural History study) who were under twelve years of age.*

a) The degree of metabolic complications in PL patients can be more varied than GL patients with some patients being treated adequately with lifestyle modifications and use of available symptomatic anti-diabetic and lipid-lowering treatments. However, other PL patients, who have more elevated HbA1c and triglycerides, despite the use of available treatments, have significant morbidity and mortality risk and require more mechanistically-based therapy aimed at the underlying leptin deficiency. While the failure of PL patients to achieve adequate metabolic control with standard treatment is not part of the eligibility criteria for the NIH studies 991265/200110769, the PL subgroup analysis is reflective of the licensed population. The EMA issued a licence specifying that metreleptin was licenced for use in PL patients in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control (23).

The data from the pivotal trials indicate that metabolically more severely affected PL patients benefitted most from the leptin replacement therapy. Patients in the PL subgroup had uncontrolled metabolic HbA1c and/or triglycerides even though the vast majority were on background medications for the treatment of these metabolic abnormalities. An analysis of the baseline characteristics of the PL subgroup in the same population as used for the NIH follow-up in the indirect treatment comparison (n=105) is provided in Table 8. This shows the use of anti-diabetic medications and lipid-lowering medications, alongside the HbA1c and triglyceride levels at baseline. In studies NIH 991265/20010769, 30 (97%) of the 31 patients in the PL subgroup were on anti-diabetic medications at baseline including 18 (58%) patients on insulin (Table 8). Similarly, 26 (84%) of the 31 PL subgroup patients were on lipid-lowering medications at baseline, including 13 (41%) patients on 2 or more lipid-lowering medications. Despite use of these symptomatic therapies, the mean metabolic response levels as measured by HbA1c and fasting serum triglycerides were still very high indicating uncontrolled diabetes and / or hypertriglyceridemia. The mean fasting serum triglyceride level in the PL subgroup was above 1,000 mg/dL which is associated with an extremely high risk of pancreatitis.

Almost all patients were receiving supportive care treatment, and yet the mean metabolic response levels as measured by HbA1c and triglycerides were still very high indicating uncontrolled diabetes and / or hypertriglyceridemia. As such, the PL subgroup is representative of those where standard treatments have failed to achieve adequate metabolic control.

Table 8: Post-hoc analysis of baseline characteristics in studies NIH 991265/20010769, PL subgroup

Baseline medications	PL subgroup (N=31), n (%)	Baseline HbA1c, % (mean, SD)	Baseline triglycerides, mg/dL (mean, SD)
Anti-diabetic medications	30 (96.8)	9.1 (1.8)	1,810.5 (2,869.6)
Insulin	18 (58.1)	8.8 (1.9)	1,340.7 (2,312.3)
Lipid-lowering	26 (83.9)	8.6 (1.7)	1,141.1 (1,794.7)
Abbreviations: HbA1c, Haemoglobin A1c; GL, Generalised lipodystrophy; PL, Partial lipodystrophy; SD, Standard deviation			

b) The number of GL patients in each key study who are under 2 years old are summarised in

Table **9**. For metreleptin studies, age is recorded at date of metreleptin initiation. For the GL/PL Natural History study age is recorded at date of diagnosis.

With respect to the indirect treatment comparison for HbA1c, there were very few GL patients who were under 2 years old with complete HbA1c data to be included in the analysis. This comprised of only 1 patient from the NIH follow-up study and 1 patient in the GL/PL Natural History study.

Table 9: Age categories of GL patients in key studies

Age category	NIH 991265/20010769, n(%)*	NIH follow-up study, n(%)**	FHA101, n(%)	GL/PL Natural History study, n(%)
Total	66 (100)	68 (100)	9 (100)	81 (100)
<2 years old	1 (1.5)	1 (1.5)	0	27 (33.3)
≥2 years old	65 (98.5)	67 (98.5)	9 (100)	54 (66.7)
Abbreviations: GL, Generalised lipodystrophy; NIH, National institutes of health; PL, Partial lipodystrophy *107 patients were used as per the Safety Analysis Set **112 patients were included as per the full NIH follow-up study population				

It is important to note that the glucose metabolism derangements will rarely develop in GL patients under 2 years old. In a systematic literature review including 1,141 lipodystrophy patients with an onset of lipodystrophy at <18 years old from 351 studies, the mean age at onset of fat loss was 0.3 years (range, 0.0 to 12 years) and 5 years (range, 0.0 to 15 years) for congenital generalised lipodystrophy (CGL) and acquired generalised lipodystrophy (AGL), respectively. The presence of diabetes mellitus was reported in 48% and 70% of CGL and AGL patients, respectively. However, the mean age ± standard deviation (range) of diabetes mellitus was 5.3 ± 5.8 (0.1–34.0) and 16.2 ± 12.9 (1.3–62.0) in CGL and AGL, respectively (25).

c) The number of PL patients in each key study who are under 12 years old are summarised in Table 10.

With respect to the indirect treatment comparison for HbA1c, there were very few PL patients who were under 12 years old with complete HbA1c data to be included in the analysis. This comprises of 2 patients from the NIH follow-up study and none from the GL/PL Natural History study.

Table 10: Age categories of PL patients in key studies

Age category	NIH 991265/20010769, n(%)*	NIH follow-up study, n(%)**	FHA101, n(%)	GL/PL Natural History study, n(%)
Total	41 (100)	44 (100)	32 (100)	149 (100)
<12 years old	2 (4.9)	2 (4.5)	0	15 (10.1)
≥12 years old	39 (95.1)	42 (95.5)	32 (100)	134 (89.9)
Abbreviations: GL, Generalised lipodystrophy; NIH, National institutes of health; PL, Partial lipodystrophy *107 patients were used as per the Safety Analysis Set **112 patients were included as per the full NIH follow-up study population				

It is important to note that the glucose metabolism derangements will rarely develop in PL patients under 12 years of age. In a systematic literature review including 1,141 lipodystrophy patients with an onset of lipodystrophy at <18 years of age from 351 studies, the mean age at onset of fat loss was 9.9 years (range, 0.0 to 16 years), and 8.2 years (range, 0.5 to 16 years) for familial partial lipodystrophy (FPLD) and acquired partial lipodystrophy (APL), respectively. The presence of diabetes mellitus was reported in 53% and 35% in FPLD and APL, respectively. The mean age ± standard deviation (range) of onset of diabetes mellitus was 24.2 ± 12.7 (8–57) and 14.8 ± 5.5 (3–22) in FPLD and APL, respectively (25).

A13. The CS reports the effects of metreleptin treatment on triglyceride levels as percentage change (e.g. CS, Tables 21 to 23). Please provide mean (SD) at baseline and endpoint, and mean (SD) absolute change, for all continuous outcome measures.

Percent change from baseline is used to describe the triglyceride outcome in the company submission. For studies NIH 991265/20010769, absolute change from baseline in triglyceride is shown in Table 11.

Table 11: Co-primary triglycerides endpoint in NIH studies 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 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**	61	29	39
	Mean (SD)	14.7 (25.66)	15.7 (26.42)	12.5 (23.35)
Month 12 value, LOCF	**n**	58	27	36
	Mean (SD)	4.5 (6.10)	6.0 (8.41)	5.4 (7.37)
Effect size: absolute change from baseline	**n**	57	27	36
	Mean (SD)	-10.3 (22.51)	-9.66 (20.30)	-7.06 (18.0)
	95% CI	4.59, 16.02	1.94, 17.38	1.23, 12.90

Abbreviations: CI, Confidence interval; FAS, Full analysis set; GL, Generalised lipodystrophy; 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

For subgroup analyses presented in the company submission, the Month 12 absolute change from baseline in triglycerides is shown in Table 12.

Table 12: Subgroup analyses for absolute Month 12 change from baseline in triglycerides for NIH studies 991265/20010769

	GL		PL subgroup[a,b]	
	Triglycerides		Triglycerides	
	N	Mean (SD) absolute Δ to Month 12	N	Mean (SD) absolute Δ to Month 12
Baseline HbA1c (%):				
<6.5	14	-0.9 (2.52)	2	-7.0 (1.95)
≥6.5	43	-14.2 (26.01)	25	-10.8 (21.6)
≥7	43	-14.2 (26.01)	23	-11.6 (22.37)
≥8	37	-15.7 (27.69)	18	-14.7 (24.54)
Baseline triglycerides (mmol/L):				
<2.26	13	0.1 (0.73)	3	-0.4 (0.6)
≥2.26	45	-13.9 (25.45)	24	-11.8 (21.75)
≥5.65	24	-25.3 (30.66)	15	-18.5 (25.44)
Lipodystrophy type				
Congenital/ Familial	39	-7.1 (16.75)	23	-11.4 (22.33)
Acquired	18	-19.2 (32.45)	4	-5.2 (6.49)
Age (years)				
< 6	5	-1.1 (2.71)	0	NA
≥6 to <12	11	-1.0 (2.16)	0	NA
≥12 to <18	23	-13.8 (23.23)	5	-26.8 (34.94)
≥18	18	-16.1 (30.84)	22	-6.8 (15)
Region[c]				
US	34	-13.5 (27.48)	20	-9.9 (19.31)
EU and EM	11	-6.0 (7.68)	2	-0.04 (1.68)
EU	7	-2.0 (2.62)	1	1.2 (NA)
Other	11	-8.7 (20.54)	5	-17.3 (30.35)

Abbreviations: Δ, change; EU, European Union, EM, Eastern Mediterranean; FAS, Full Analysis Set; GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; LOCF, Last observation carried forward; NA, Not-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 (NIH studies 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

For FHA101, absolute change from baseline in triglyceride is shown in Table 13.

Table 13: Co-primary triglycerides endpoint in 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 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: absolute change from baseline	**n**	5	7	26
	Mean (SD)	-21.43 (38.86)	-0.43 (1.49)	-2.80 (10.36)
	95% CI	-26.82, 69.68	-0.95, 1.81	-1.38, 6.99

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CI, Confidence interval; FAS, Full analysis set; GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; 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

For the Addenbrooke's EAP, absolute change from baseline in triglyceride is shown in Table 14.

Table 14: Results from Early Access Programme at Addenbrooke's Hospital

Study name		Addenbrooke's Hospital Early Access Programme data		
Size of study groups	**Treatment**	GL = 10 PL subgroup[a] = 18 PL overall = 21		
Study duration	**Time unit**	Ongoing		
Change from baseline in triglycerides (mmol/L)				
		GL N = 10	PL subgroup[a] N = 18	PL overall N = 21
Baseline value	**n**	10	17	20
	Mean (SD)	6.4 (5.06)	4.7 (5.74)	4.2 (5.40)
Month 12 value[b]	**n**	7	5	6
	Mean (SD)	4.6 (4.21)	3.2 (2.18)	3.2 (1.96)
Month 36 value[c]	**n**	3	4	5
	Mean (SD)	4.1 (4.91)	1.8 (1.83)	1.6 (0.69)
Effect size: absolute change from baseline at Month 12[b]	**n**	7	4	5
	Mean (SD)	-3.5 (1.90)	-0.8 (0.79)	-0.6 (0.84)
Effect size: absolute change from baseline at Month 36[c]	**n**	3	3	4
	Mean (SD)	-3.4 (2.15)	-0.7 (1.32)	-0.6 (1.08)

Abbreviations: GL, Generalised lipodystrophy; 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]Defined as the 4th visit (Month 12) to Addenbrooke's Hospital where the 1st visit is at baseline i.e. metreleptin initiation.
[c]Defined as any visit to Addenbrooke's Hospital between Month 30 and Month 42

A14. Priority Question: *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: 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 antidiabetic and lipid lowering drugs; liver cirrhosis; hyperphagia; 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 these in your response.

Regarding the outcomes listed above, for each of the key metreleptin studies additional information can be found in:

- NIH 991265/20010769 – As adverse events (AEs) in Section 12 of the clinical study report (CSR) (9). Owing to limitations in the understanding of the disease at the initiation of the study, these outcomes were recorded as adverse events only.
- NIH follow-up study – Tables 2-7 of the technical report (10)
- FHA101 – As AEs in Section 12 of the CSR (26)
- Addenbrooke's Early Access Programme (EAP) – Tables 27 and 28 of the technical report (17). In addition to the analyses presented in the technical report, Addenbrooke's have collected additional patient-level data regarding follow-up organ damage and other complications, however, this data is incomplete. This is because Addenbrooke's Hospital is the main centre of care for lipodystrophy patients in England, and therefore many of its patients are travelling from all across England to attend care and treatment at this Hospital, but their main residence remains outside of Cambridge. Addenbrooke's Hospital did not have access to patient record files in other hospitals and General Practitioner (GP) surgeries when collecting the EAP data to be able to complete the full patient history data with regards to complications and organ damage.

With regards to the mortality outcome, it is known that since the inception of the Addenbrooke's EAP, 2 of the 10 GL patients participating have died, and 2 of the 21 PL patients participating have died.

Owing to the limitations of retrospective data collection in a tertiary setting, data missingness means that no analysis can be performed on this data to provide any valuable insight. As such, Addenbrooke's Hospital have reviewed their current data collection and have set up an enhanced data collection for patients receiving metreleptin from the anticipated date of NICE issuing a positive recommendation for the use of metreleptin (January 2021) (27). This data

collection will be part of the clinical care pathway and will be made available to NHS England on a regular basis; EClip and its registry also supports the data collection requirements in relation to the EMA's exceptional circumstances authorisation of metreleptin.

Data for these outcomes from other, smaller metreleptin studies is presented in Appendix 1: Additional data for lipodystrophy outcomes from smaller metreleptin studies (in response to A14).

A15. Priority Question: *Section 9.4.3 (CS, Tables 16 to 18) includes details of the numbers of patients, in studies NIH 991265/20010769 and FHA101 and the Addenbrooke's EAP, taking antidiabetic and lipid lowering medication. Please provide the numbers of patients, in studies NIH 991265/20010769 and FHA101 and the Addenbrooke's EAP, who remained on antidiabetic medication and who remained on lipid lowering medication, at 12 months or the relevant end point.*

NIH studies 991265/20010769

For NIH studies 991265/20010769, a post-hoc analysis was performed in the same population as used for the NIH follow-up in the indirect treatment comparison (n=105) regarding insulin, antidiabetic medications or lipid-lowering medication at Month 12 compared to baseline (Table 15). There was a reduction in the use of anti-diabetic or lipid-lowering medications (i.e. supportive care). This is consistent with the conclusions reached by the Delphi Panel, which agreed that supportive care medications can be discontinued or their dose reduced in some lipodystrophy patients receiving metreleptin (see Section 12.3.6 in company submission, pages 199 to 201). Despite this reduction in the use of supportive care, statistically and clinically meaningful reductions in HbA1c and triglycerides were observed in patients at Month 12 compared to baseline in the NIH studies 991265/20010769.

At baseline, 88 lipodystrophy patients were on antidiabetic medications, including insulin. At Month 12, 28 (31.8%) of these patients discontinued anti-diabetic medications, thus 60 (68.2%) of these patients remained on anti-diabetic medications. Specifically, 58 patients were using insulin at baseline. At Month 12, 29 (50.0%) of these patients discontinued insulin at Month 12, thus 29 (50.0%) remained on insulin.

At baseline, 66 lipodystrophy patients were on lipid-lowering medications. At Month 12, 32 (48.5%) of these patients discontinued lipid-lowering medications, thus 34 (51.5%) remained on lipid-lowering medications.

Table 15: Baseline anti-diabetic and lipid-lowering medications at baseline and at 12 months in NIH studies 991265/20010769

Baseline medication	N	Medication continued at 12 months, N(%)	No medication at 12 months, N(%)
Any concomitant medications	94	68 (72.3)	26 (27.7)
Anti-diabetic medications	88	60 (68.2)	28 (31.8)
Insulin	58	29 (50.0)	29 (50.0)
Lipid-lowering medications	66	34 (51.5)	32 (48.5)

FHA101

The primary intent of this treatment investigational new drug (IND) study was not hypothesis testing, but to provide access for lipodystrophy patients. Given the limited sample size for this supportive study (9 patients with GL and 7 patients in the PL subgroup), it is expected that the changes from baseline to Month 12/LOCF, which were directionally consistent with the larger primary NIH studies 991265/20010769, did not reach statistical significance (26).

In FHA101, data for all anti-diabetic or lipid-lowering medications, 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 Controlled Concomitant Medication Full Analysis Set (CFAS). The CFAS included all patients in the Full Analysis Set who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid-lowering medications), prior to Month 12. The Controlled Concomitant Medication Efficacy-Evaluable Analysis Set (CEEAS) which included all patients in the CFAS who have either primary efficacy parameter of interest measured at Month 12 and have no major protocol violations prior to Month 12 (Table 16) (26).

Table 16: Datasets analysed in FHA101

Analysis Sets	GL	PL	
	(N=9)	PL Subgroup (N=7)	Overall (N=32)
Safety Analysis Set[b]	9 (100.0)	7 (100.0)	32 (100.0)
Full Analysis Set[c]	9 (100.0)	7 (100.0)	29 (90.6)

Controlled CM Full Analysis Set[d]	2 (22.2)	6 (85.7)	18 (56.3)
Controlled CM Efficacy-Evaluable Analysis Set[e]	2 (22.2)	5 (71.4)	9 (28.1)

Abbreviations: CM, Concomitant medication; GL, Generalised lipodystrophy; 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: FHA101 CSR (26)
[b] All enrolled patients who received at least 1 dose of study drug.
[c] All patients in the Safety Analysis Set who have either primary efficacy parameter measured at baseline and at ≥1 post-baseline visit.
[d] All patients in the Full Analysis Set who have controlled concomitant medication use prior to Month 12.
[e] All patients in the Controlled CM Full Analysis Set who have either efficacy parameter of interest measured at Month 12 and have no major protocol violations prior to Month 12.

In FHA101, only 2 GL patients received anti-diabetic and lipid-lowering drugs at baseline and remained on therapy after Month 12. Although the mean HbA1c decreased from 7.9% at baseline to 4.7% at Month 12 in the GL patients part of the CFAS, this result did not reach statistical significance due to the very low number of patients. In addition, fasting triglycerides (mean) were reduced in these two GL patients from 12.4 mmol/L at baseline to 2.8 mmol/L at Month 12. Similarly, only 6 patients in the relevant PL subgroup received anti-diabetic or lipid-lowering drugs at baseline and remained on treatment at Month 12. Mean HbA1c was 7.2% at baseline and 7.1% at Month 12, with the results not reaching statistical significance (26).

Addenbrooke's Early Access Programme

For the Addenbrooke's EAP, data is available for 20 patients regarding those who remained on insulin, antidiabetic medications or triglyceride lowering medication at Month 12 (Table 17) (17). Mean (SD) baseline insulin dose was 167.1 (72.2) IU/day, decreasing to 103 (48.4) IU/day at Month 12. Mean (SD) number of baseline antidiabetic medications was 1.2 (0.4) and patients either decreased, discontinued (2 patients) or had no change in their antidiabetic medications (13 patients) at Month 12. Mean (SD) number of baseline triglyceride lowering medications was 1.3 (0.6) and all (9 patients) had no change from baseline in their triglyceride lowering medications at Month 12.

Table 17: Addenbrooke's EAP Concomitant Drug Use

Parameter	All Patients N = 20
Insulin	
Baseline dose (IU/day)	
Patients on treatment (N)	10
Mean (SD)	167.1 (72.2)
[Median]	[176]
{Min, Max}	{35, 280}
Month 12 dose (IU/day)[a]	
Patients on treatment (N)	7
Mean (SD)	103 (48.4)
[Median]	[118]
{Min, Max}	{41, 152}
Antidiabetic medications	
Baseline number of medications (n)	
Patients on treatment (N)	17
Mean (SD)	1.2 (0.4)
[Median]	[1]
{Min, Max}	{1, 2}
Month 12 number of medications (n)[a,b]	
Patients with Month 12 data (N)	15
Change from baseline to Month 12	
Increased	0
Decreased/ discontinued	2
No change	13
Inconclusive[c]	0
TG lowering medications	
Baseline number of medications (n)	
Patients on treatment (N)	3
Patients not on treatment (N)[d]	6
Mean (SD)	1.3 (0.6)
[Median]	[1]
{Min, Max}	{1, 2}
Month 12 number of medications (n)[a,b]	
Patients with Month 12 data (n)	9
Change from baseline to Month 12	
Increased	0
Decreased	0
No change	9

Abbreviations: EAP, Expanded access programme; GL, Generalised lipodystrophy; IU, International unit; PL, Partial lipodystrophy; SD, Standard deviation; TG, Triglycerides.

Source: Technical Report: Real-World Experience of Generalized and Partial Lipodystrophy Patients Enrolled in the Metreleptin Early Access Program (17)

[a]Month 12 values were captured within month 4 to month 16, set as the values closest to month 12 within the range.

[b] Number of medications is not available for follow-up visits.

[c] Patients who had an increase and decrease of number of medications from baseline to month 12 were considered as inconclusive.
[d]Patients with both baseline and Month 12 data.

A16. 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,
c) how long they have been followed up.

Please provide these data for all key studies included in the CS NIH 991265/20010769 (NCT00025883), FHA101 (NCT00677313), NIH Follow-Up study and GL/PL Natural History study).

Details regarding the number of UK patients are described in Table 18. For study FHA101, it is unknown how many patients were from the UK as this was not recorded as part of the clinical trial data. Despite the low numbers of UK patients in the key studies, it was stated in the original Final Evaluation Decision (FED) that "the clinical experts confirmed that the trial populations were generalisable to patients seen in clinical practice in England" (14).

Table 18: Summary of UK patients in key studies

UK Patients	**NIH 991265/20010769 (n=107)***	**NIH follow-up study (n=112)***	**FHA101 (n=41)**	**GL/PL Natural History study (n=230)****
Number of UK patients, n(%)	2 (1.9)	2 (1.8)	-	1 (0.4)
Duration of metreleptin treatment, years	Patient 1: 7.40 Patient 2: 0.68	Patient 1: 7.40 Patient 2: 0.68	NA	NA
Duration of follow-up, years	Patient 1: 7.40 Patient 2: 0.68	Patient 1: 7.40 Patient 2: 0.68	NA	16.31

Abbreviations: GL, Generalised lipodystrophy; NIH, National institutes of health; NA, Not applicable; PL, Partial lipodystrophy; UK, United Kingdom.
* The UK patients in studies NIH 991265/20010769 and the NIH follow-up study were the same. These two patients were followed as part of these studies until discontinuing (one patient was transferred to another programme and the other was determined as ineligible).
** The follow-up period spanned the time from date of diagnosis with GL or PL until loss to follow-up, death, or date of chart abstraction, whichever occurred first.

A17. On page 106 of the CS it states: *'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.'
If the correlation between the tests was not taken into account, the conclusion is biased because of the reduced power of the test.

a) Please provide details on how the inflation of the type II error was controlled for in the NIH trials given that the primary efficacy analysis is based on co-primary endpoints.

b) What is the dependency between the two test statistics for Hb1Ac and TG?

a) The analysis for NIH studies 991265/20010769 was performed in 2016/2017. Based on the Statistical Analysis Plan, version 2.0 dated 07 September 2016, the sample size justification read as follows:

As Studies 991265 and 20010769 are both completed with a total of 107 patients enrolled, sample size justification is not required. However, the NIH investigators specified a sample size justification in both study protocols as follows:
"Based on preliminary data in a cross-sectional study, the mean ± SD HbA1c data for 8 patients with generalised lipodystrophy was 9.1±2.2%. Based on assumption of a 1.5% (for protocol 991265 and 1.0% for 20010769) actual decrease in HbA1c levels over a period of 4 months (for protocol 991265 (and 12 months for 20010769) as clinically meaningful, 10 patients would be required for 80% study power and an alpha error of 5%. Also, based on previous cross-sectional data, the mean ± SD fasting triglyceride levels for 8 patients with generalised lipodystrophy was 2200±900 mg/dL. Based on assumption of 660 mg/dL (or 30% decrease from the mean baseline) decrease as clinically meaningful, 10 patients with hypertriglyceridemia would be required for 80% study power and 5% alpha error."
Upon validation of the sample size calculation, it was found that based on the assumptions above, 32 patients would be required in order to detect a 1% actual decrease in HbA1c and 15 patients would be required in order to detect a 1.5% actual decrease in HbA1c with 80% power and 5% one-sided alpha error. For triglycerides, a sample size of 13 would be required to detect a reduction of 660 mg/dL with 80% power and 5% one-sided alpha error. As noted, the final sample size across the 2 protocols was 107 patients. As it became clear that treatment with metreleptin was improving the metabolic abnormalities associated with lipodystrophy and could be safely administered with long-term benefit to patients, the protocol was amended to expand the eligibility criteria and to increase the sample size.

The actual power of NIH studies 991265/20010769 for each endpoint separately, for each lipodystrophy type, is listed in Table 19.

Table 19: Power of NIH studies 991265/20010769 for each co-primary endpoint

Parameter	Lipodystrophy Type	Sample Size (Evaluable at Month 12)	Actual Power
HbA1c	Generalised	59	0.92964
HbA1c	Partial	37	0.76746
Triglycerides	Generalised	57	0.99975
Triglycerides	Partial	37	0.99132

If the two parameters are completely uncorrelated (most conservative approach), this results in a minimum power of declaring success in this study of 0.92964 × 0.99975 = 0.9294 for generalised lipodystrophy and 0.76746 × 0.99132 = 0.7608 for partial lipodystrophy. (Note that the parameters are, in fact, correlated, and so the actual combined powers are >0.9294 and >0.7608 for generalised and partial, respectively).

b) Test statistics are not random variables; they are single points of the distribution based on the degrees of freedom. Therefore, test statistics are, by definition, independent.

However, with regards to the correlation between HbA1c and triglyceride values at Month 12, we can look at the Pearson correlation coefficients in Table 20.

Table 20: Pearson correlation coefficients between HbA1c and triglyceride at Month 12

Lipodystrophy Type	Pearson Correlation Coefficient	P-value
Generalised	0.68164	<0.0001
Partial	0.41274	0.01

In both lipodystrophy types, values of HbA1c and triglycerides at Month 12 are positively correlated.

A18. Please provide additional details on the last information carried forward (LOCF) analysis of the NIH 991265/20010769 (NCT00025883) study,

including the pattern of missingness of the outcome at 12 months and the gap between 12 months and the last information on Hb1Ac and fasting TG.

Below is a table of patients with missing Month 12 values by parameter and lipodystrophy type, for the Full Analysis Set (n=102) in NIH studies 991265/20010769 Table 21.

Table 21: Missing Month 12 values by parameter in NIH studies 991265/20010769

Parameter	Lipodystrophy Type	# of Missing Month 12 Values	# of LOCF Month 12 Values
HbA1c	Generalised	21	18
HbA1c	Partial	9	6
Triglycerides	Generalised	21	17
Triglycerides	Partial	9	6

The mean duration between the previous non-missing timepoints and the Month 12 LOCF carry over for these patients are shown in Table 22.

Table 22: Mean duration between the previous non-missing timepoints and the Month 12 LOCF

Parameter	Lipodystrophy Type	Mean (SD) Duration (in days) between Month 12 and LOCF timepoint
HbA1c	Generalised	136.5 (31.54)
HbA1c	Partial	141.8 (32.26)
Triglycerides	Generalised	135.8 (32.35)
Triglycerides	Partial	141.8 (32.26)

These results suggest that the Month 8 visit (which occurred 120 ± 30 days prior to the Month 12 visit) was, more often than not, used for the LOCF if Month 12 was missing.

As for the missing pattern for HbA1c and triglycerides up to Month 12, they can be found in Appendix 2: Missingness pattern for HbA1c and triglycerides up to Month 12 in NIH studies 991265/20010769 (in response to A18), Table 53-Table 56. (all based on the Full Analysis Set). An 'X' symbol refers to the value being present, whereas the '.' refers to the value being missing. Additionally, the intervals for the analysis visits are presented in Appendix 2: Missingness pattern for HbA1c and triglycerides up to Month 12 in NIH studies 991265/20010769 (in response to A18)Appendix , Table 52 for convenience.

Note that other than the Month 6 visit, all other visits were protocol-specified, in both 991265 and 20010769 protocols.

A19. *Akinci et al. (2019) highlighted several limitations of the Natural History study in the discussion session of their publication. Please comment on these limitations and what impact they might have had on the presented analysis.*

Akinci *et al.* (2019) highlights that the study population was limited to patients who have never received lipodystrophy specific therapies, therefore the reported lifetime prevalence rates of complications, such as metabolic abnormalities, are likely to be an underestimate for the broader patient population that have received lipodystrophy specific therapies (12). This was addressed in our analyses by controlling the propensity score model for covariates which accounted for severity, for instance age. However, it is possible that our average treatment effects (ATEs) remain an underestimate of the effect of metreleptin.

Some parameters – for instance, the severity of organ abnormalities – were not reliably captured in patient medical charts, therefore the study only provides a simplified view of disease progression in lipodystrophy. This meant that our indirect treatment comparison could not incorporate the severity of organ damage and disease progression at a specific organ level. The natural history study did intend to explore disease burden, but not all data from primary care physicians (including data on comorbidities, laboratory results and organ abnormalities, and medication use prior to intake at the centres) were collected as part of a formal systematic algorithm, also limiting the extent to which these factors could be incorporated into our analyses, and reducing the number of patients we could incorporate into our analyses – specifically those exploring the change in HbA1c.Finally, an intrinsic limitation of the study design was the nature of medical chart review which relies on the accuracy of data recorded in patient medical charts and online forms. This leaves room for error, and therefore becomes an unavoidable form of potential inaccuracy in our results.

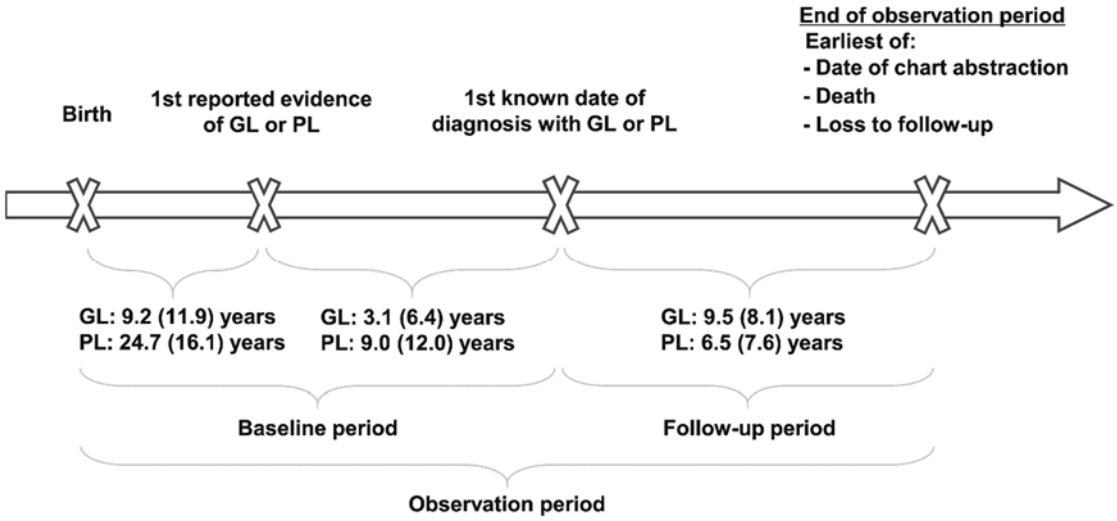
Evidence synthesis and meta-analysis

A20. *On page 138 of the CS, the company stated that 'In the GL/PL Natural History study, baseline was defined as ± 3 months from the date of diagnosis.' Whilst in the publication by Akinci et al. any time prior to the initial diagnosis of GL or PL was defined as the 'baseline period,' and any time on or following this diagnosis was defined as the 'follow-up period.' Does this mean that the company re-define the baseline? Also what is the definition of baseline in the NIH follow-up study?*

In the GL/PL Natural History study, the baseline period was defined as any time prior to the initial diagnosis of GL or PL as shown in

Figure 1 below (Figure 17 in the CS). As such, the baseline period covered a long time – from birth to lipodystrophy diagnosis. For example, the mean time from birth to first reported evidence of GL or PL was 9.2 or 24.7 years, respectively, and then a further 3.1 or 9.0 years from first reported evidence of GL or PL to diagnosis of lipodystrophy, respectively.

Figure 1: Study design of the GL/PL Natural History Study



Abbreviations: GL, Generalised lipodystrophy; PL, Partial lipodystrophy. Years are given as mean (standard deviation).

Source: Akinci 2019 (12)

In the NIH follow-up study, baseline was defined as the date of metreleptin initiation: triglyceride and HbA1c measurements were taken at this date. As no

alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measurements were taken explicitly at the baseline date, this was defined as ± 3 months from the date of metreleptin initiation to maximise the amount of data that could be utilised in the indirect treatment comparison analyses.

A similar approach was taken when defining baseline in the GL/PL Natural History study. Though the date of baseline as defined by Akinci *et al.* was any time prior to lipodystrophy diagnosis, we can confirm it was redefined as ± 3 months from the data of lipodystrophy diagnosis to more closely align it to the definition of baseline used in the NIH follow-up study. This approach was validated by clinical experts at Addenbrooke's Hospital. Furthermore, eligibility for metreleptin requires a confirmed diagnosis of lipodystrophy.

A21*. Priority question: For the GL/PL natural history study, please provide full results for the key outcome measures (baseline, follow-up and change from baseline HbA1c, triglycerides, lipids, liver enzymes), analogous to the results provided for NIH 991265/20010769 (Table 21, Section 0.6 of the CS).*

The GL/PL Natural History study is an international chart review. Its objective was to explore the documentation of organ system abnormalities affected by the pathophysiological adaptation mechanisms associated with metabolic abnormalities. As such, these key laboratory measures such as HbA1c and triglyceride were not explicitly reported at baseline and outcome timepoints in the GL/PL Natural History study publication, Akinci *et al.* 2019 (12). However, we can use the patient-level data used in our ITC analyses we can provide baseline, outcome and change from baseline results for HbA1c, triglycerides and liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) for patients with data at both the baseline timepoint (± 3 months from the date of lipodystrophy diagnosis, as reported in response to A20) and the outcome timepoint (1 year ± 6-months from the date of diagnosis). These are summarised in Table 23. Compared to the NIH follow-up study (Table 21 in the CS), changes are generally less substantial for all endpoints in the GL/PL Natural History study: for instance in GL and PL subgroup patients respectively, HbA1c values in the NIH follow-up study had a mean -2.2% and -

0.9% actual change from baseline to outcome (9), compared to -0.31% in the GL/PL Natural History study.

Table 23: Key outcome measures in GL/PL Natural History study used in indirect treatment comparison analyses

HbA1c (%)		
Baseline value (± 3 months from date of diagnosis)	**n**	21
	Mean (SD)	7.49 (1.97)
Outcome value (1 year ± 6 months from date of diagnosis)	**n**	21
	Mean (SD)	7.18 (1.75)
Effect size: actual change from baseline (ITC)	**n**	21
	Mean (SD)	-0.31 (1.38)
	95% CI	-0.94, 0.32
Triglycerides (mmol/L)		
Baseline value (± 3 months from date of diagnosis)	**n**	46
	Mean (SD)	380.25 (442.62)
Outcome value (1 year ± 6 months from date of diagnosis)	**n**	46
	Mean (SD)	300.26 (335.91)
Effect size: actual change from baseline (ITC)	**n**	46
	Mean (SD)	-79.98 (411.67)
	95% CI	-202.23, 42.27
ALT (U/L)		
Baseline value (± 3 months from date of diagnosis)	**n**	42
	Mean (SD)	43.42 (30.83)
Outcome value (1 year ± 6 months from date of diagnosis)	**n**	42
	Mean (SD)	43.13 (30.03)
Effect size: actual change from baseline (ITC)	**n**	42
	Mean (SD)	-0.29 (32.97)
	95% CI	-10.57, 9.98
AST (U/L)		
Baseline value (± 3 months from date of diagnosis)	**n**	38
	Mean (SD)	35.78 (19.21)

Outcome value (1 year ± 6 months from date of diagnosis)	**n**	38
	Mean (SD)	32.52 (18.68)
Effect size: actual change from baseline (ITC)	**n**	38
	Mean (SD)	-3.27 (17.88)
	95% CI	-9.14, 2.61
Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CI, Confidence interval; HbA1c, Haemoglobin A1c; ITC, Indirect treatment comparison; SD, Standard deviation.		

A22. *In section 9.3.1 of the CS the company stated that 'There were 38 observational references which evaluated metreleptin as an intervention, covering 12 clinical studies, 35 observational references which did not include metreleptin as an intervention, and one randomised controlled trial (RCT) which compared Cholic Acid therapy with placebo. There were no references identified which compared metreleptin to standard of care alone.' Please explain the reason for using only the NIH Follow-up trial for the treatment arm and the GL/PL Natural History study for the comparator arm. Was there the possibility of using other indirect comparison methods, as MAIC, considered in order to include the other studies?*

Please refer to our response to question A10 which provides further details of the systematic review and the explanation of which studies were suitable for inclusion in the indirect treatment comparison.

The GL/PL Natural History study was identified through a clinical systematic literature review (SLR) as the most appropriate supportive care (SC) arm for this analysis as it comprised the largest cohort of the main four forms of lipodystrophy patients (also included in the NIH trials) who are naïve to leptin as the only available lipodystrophy-specific therapy. Patient-level data were obtained and therefore allowed for adjustments in populations to be accounted for using methods like inverse probability weighting (IPW) rather than relying on aggregate comparator data.

Other studies were considered for use as a comparator arm - such as the TuLip study (24) - however this had a substantially smaller sample size (n=33) and included only patients with congenital generalised lipodystrophy (CGL) representing only one of the main four forms of lipodystrophy.

NIH studies 991265/20010769 were considered the main clinical trials by the European Medicines Agency (EMA) in their assessment of metreleptin and comprised the largest and most robust data set of all metreleptin studies considered. The NIH follow-up study extended the 991265/20010769 study by undertaking a chart review to collect long-term data and additional outcomes for lipodystrophy patients included in the original study who received metreleptin therapy at the NIH. This long-term data from the NIH follow-up study was used for the metreleptin data in the indirect treatment comparison where individual patient level data was available (10). For instance, only one other single arm study – Zadeh *et al.* 2013 (28) – considered patients with all four main forms of lipodystrophy (acquired generalised lipodystrophy [AGL], acquired partial lipodystrophy [APL], congenital generalised lipodystrophy [CGL], familial partial lipodystrophy disease [FPLD]). However, this study comprised only 27 patients. Furthermore, as individual patient-level data (PLD) were available for both the NIH follow-up study and the GL/PL Natural History study, these were deemed the most appropriate studies for the indirect treatment comparison (ITC).

A matched-adjusted indirect comparison (MAIC) was not considered as PLD were available for both the studies in question. Thus, inverse probability weighting (IPW) was deemed to be superior to an analysis relying on aggregate comparator data: IPW provides a means to adjust for differences in baseline population characteristics when generating clinical effectiveness estimates. In addition, further sensitivity analyses have been conducted using IPW with regression adjustment (IPW+RA) utilising alternate statistical software (STATA IC 16.1) to confirm the robustness of the results and from the IPW ITC. The results are reported in Table 24,

Table ***25***, Table 26,

Table ***27***, Table 28 and Table 29. These sensitivity analyses were not performed for the mortality outcome, as the model resulted in problems with convergence and overfitting, and therefore could not produce reliable treatment effect estimates.

Table 24: ATE of metreleptin with or without supportive care versus supportive care alone using IPW + RA, trimming at 1% level in HbA1c change from baseline to Month 12

	Coefficient (mean HbA1c, %)	**Robust standard error**	**95% CI**	**p-value**
ATE of metreleptin with or without SC versus SC	-2.42	0.27	-2.95; -1.88	**<0.001***
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; IPW – Inverse probability weighting; RA – Regression adjustment; SC, Supportive care * denotes significance at the P<0.05 level				

Table 25: ATE of metreleptin with or without supportive care versus supportive care alone using IPW + RA in triglyceride change from baseline to Month 12. mmol/L results given in square brackets by dividing by 88.5.

	Coefficient (mean triglycerides, mg/dl [mmol/l])	**Robust standard error**	**95% CI**	**p-value**
ATE of metreleptin with or without SC versus SC	-902.71 [-10.20]	222.57 [2.51]	-1338.94; -466.50 [-15.13; -5.27]	<0.001*
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; IPW – Inverse probability weighting; RA – Regression adjustment; SC, Supportive care * denotes significance at the P<0.05 level				

Table 26: ATE of metreleptin with or without supportive care versus supportive care alone using IPW + RA in ALT change from baseline to Month 12

	Coefficient (mean ALT, U/L)	**Robust standard error**	**95% CI**	**p-value**

ATE of metreleptin with or without SC versus SC	-43.61	10.67	-64.52, -22.70	<0.001*
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; IPW – Inverse probability weighting; RA – Regression adjustment; SC, Supportive care * denotes significance at the P<0.05 level				

Table 27: ATE of metreleptin with or without supportive care versus supportive care alone using IPW + RA in AST change from baseline to Month 12

	Coefficient (mean ALT, U/L)	**Robust standard error**	**95% CI**	**p-value**
ATE of metreleptin with or without SC versus SC	-27.18	6.71	-40.33; -14.02	<0.001*
Abbreviations: ATE, Average treatment effect; CI, Confidence interval; IPW – Inverse probability weighting; RA – Regression adjustment; SC, Supportive care * denotes significance at the P<0.05 level				

Table 28: OR of metreleptin in pancreatitis episodes with or without supportive care versus supportive care alone using IPW + RA from baseline to Month 12

	OR (coefficient)	**Standard error**	**95% CI of OR (coefficient)**	**p-value**
ATE of metreleptin with or without SC versus SC	0.93 (-0.067)	0.025	0.89; 0.98 (-0.12, 0.018)	**0.008***
Abbreviations: OR, Odds ratio; ATE, Average treatment effect; CI, Confidence interval; IPW – Inverse probability weighting; RA – Regression adjustment; SC, supportive care * denotes significance at the P<0.05 level				

Table 29: OR of metreleptin in pancreatitis episodes when missing data is imputed with or without supportive care versus supportive care alone using IPW + RA from baseline to Month 12

	OR (coefficient)	Standard error	95% CI of OR (coefficient)	p-value
ATE of metreleptin with or without SC versus SC	0.93 (-0.075)	0.026	0.88; 0.98 (-0.12; -0.024)	**0.004***

Abbreviations: OR, Odds ratio; ATE, Average treatment effect; CI, Confidence interval; IPW – Inverse probability weighting; RA – Regression adjustment; SC, Supportive care

* denotes significance at the P<0.05 level

A23. *The NIH follow-up study was conducted in one centre in the US, whilst the natural history study in 5 centres over 3 countries. Were centre/country effects accounted for in the analysis?*

The NIH 991265/20010769 studies were conducted at the NIH, however, patients were also enrolled from countries outside the US over an extended period (see Table 14, company submission for further information). As such, patients were travelling from outside the US to participate in these studies and these can be considered international studies. In section 4.3 of the Final Evaluation Document (FED), it was noted that "*clinical experts confirmed that the trial populations were generalisable to patients seen in clinical practice in England*" (14).

Centre and country effects were not accounted for in the indirect treatment comparison analyses. As there were limited data available for use in the analyses – specifically for the GL/PL Natural History study - the addition of further covariates in the propensity score model risked overfitting the model. The location of where patients were treated and the impact this has on the ITC is explored in our response to B3.

A24*. The company have performed the naive comparison of the change from baseline for continuous outcomes using a two-sample t-test but the*

assessment of the normality of these outcomes in section 17.12.2 suggests violation of the normality distribution for all outcomes indicating that a t-test is not an appropriate statistical test. Please also provide results of indirect comparisons using a suitable non-parametric test (Mann-Whitney test) and report the treatment effect as median difference (with range or 95% CI)

Please see the results of the naïve comparison of the change from baseline between the GL/PL Natural History study using the Mann-Whitney/Wilcoxon Rank-Sum test in Table 30, Table 31, Table 32 and Table 33.

Table 30: Naïve analysis of median HbA1c change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline

Intervention (study)	**Median HbA1c change (%), at Month 12 from baseline with metreleptin with or without supportive care versus supportive care alone**	**Range**	**Absolute HbA1c difference with metreleptin with or without supportive care versus supportive care alone (%)**	**p-value**
Metreleptin with or without supportive care (NIH Follow-up study)	-1.6	-4.8; 2.1	-1.6	**<0.001***
Supportive care (GL/PL Natural History Study)	0.0	-8.1; 0.9		
Abbreviations: GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; NIH, National institutes of health; PL, Partial lipodystrophy. * denotes significance at the P<0.05 level				

Table 31: Naïve analysis of median triglyceride change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline

Intervention (study)	**Median triglyceride change (mmol/L) at Month 12 from baseline with metreleptin with or without supportive care**	**Range**	**Absolute triglyceride difference with metreleptin with or without supportive care versus**	**p-value**

	versus supportive care alone		supportive care alone (mmol/L)	
Metreleptin with or without supportive care (NIH Follow-up study)	-195.0	-11589; 3074	-162.5	**<0.001**
Supportive care (GL/PL Natural History Study)	-32.5	-1705; 1223		
Abbreviations: GL, Generalised lipodystrophy; NIH, National institutes of health; PL, Partial lipodystrophy. * denotes significance at the P<0.05 level				

Table 32: Naïve analysis of median ALT change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline

Intervention (study)	Median ALT change (U/L) at Month 12 from baseline with metreleptin with or without supportive care versus supportive care alone	Range	Absolute ALT difference with metreleptin with or without supportive care versus supportive care alone (U/L)	p-value
Metreleptin with or without supportive care (NIH Follow-up study)	-17.0	-665; 102	-16.0	**<0.001**
Supportive care (GL/PL Natural History Study)	-1.0	-133; 65		
Abbreviations: ALT, Alanine aminotransferase; GL, Generalised lipodystrophy; NIH, National institutes of health; PL, Partial lipodystrophy. * denotes significance at the P<0.05 level				

Table 33: Naïve analysis of median AST change of metreleptin with or without supportive care compared to supportive care at Month 12 compared to baseline

Intervention (study)	Median AST change (U/L) at Month 12 from baseline with metreleptin with or without supportive care versus supportive care alone	Range	Absolute AST difference with metreleptin with or without supportive care versus supportive care alone (U/L)	p-value
Metreleptin with or without supportive care (NIH Follow-up study)	-11.0	-356; 88	-8.5	**0.008***
Supportive care (GL/PL Natural History Study)	-2.5	-52; 41		
Abbreviations: AST, Aspartate aminotransferase; GL, Generalised lipodystrophy; NIH, National institutes of health; PL, Partial lipodystrophy. * denotes significance at the P<0.05 level				

A25*. In section 17.12.3.1.7 the company provide the naive comparison of mortality, please provide details of the statistical methods used to obtain both p-values as well as the 95% CI for the hazard ratio.*

R version 3.6.1 was used in order to produce a cox-proportional hazards model. The survival package was used alongside the **coxph** function to obtain p-values and 95% confidence intervals for the hazard ratio. The **survfit** function was used to assess the p-value of the difference between the hazard ratios.

A26. Please provide the model code for the ITC analysis.

The code for the indirect treatment comparison (ITC) analyses are provided in Appendix 3: ITC code (in response to A26)

A27. *On page 134 of the CS, it is stated that 'Clinician validation confirmed that the assumption of 'no unobserved confounding' was reasonable – or that patient characteristics that affect the outcomes of interest are observed and*

accounted for in the methodology.' However, later it is stated that a variety of additional covariates were considered but not deemed feasible because of missing values. Also on page 118 it is stated that in general, older patients who had higher levels of HbA1c and triglycerides at baseline had larger mean decreases from baseline than younger patients. Also, time from diagnosis to treatment/level of progression of disease might have an impact on the outcome, but on page 71 the CS states that 'Due to the ultra-rare nature of lipodystrophy, many clinicians are unfamiliar with diagnosis and management, and diagnosis can take many years. As such, patients can go through multiple healthcare checks before final diagnosis, leaving the underlying cause of their disease unmanaged and the disease progressing.' In addition to its proven efficacy in GLD, metreleptin is effective in selected PLD patients with severe metabolic derangements or low leptin (1). Given the above-mentioned issues, please further justify the assumption of no unobserved confounding and the possible impact on results.

It is possible that confounding covariates were identified during clinical study design and could not be observed. This was an inherent limitation of analyses of this type, although clinical input was sought to ensure that no major known confounders had been omitted because they were unobservable.

There is always a possibility that due to unobserved confounders the average treatment effect (ATE) may be less attributable to the treatment at hand. However, it is important to note that clinical opinion – including clinicians at Addenbrooke's hospital – identified that age, gender, and lipodystrophy type were the most important and relevant covariates to include in the propensity score model. While a sensitivity analysis using additional co-variates (history of baseline elevated HbA1c and elevated triglycerides, baseline leptin levels and baseline pancreatitis) was explored, this analysis was not feasible due to overfitting (see Section 9.8.1 in company submission). No additional unobserved co-variates were identified by clinical experts. Furthermore, a confounder has an association with both exposure and outcome. Though these listed covariates may be associated with outcomes, we do not believe they are associated with determination of treatment exposure – and thus they were not included as covariates.

A28. *Was the positivity assumption, i.e. when certain subgroups in a finite sample do not receive some of the treatment levels of interest, verified?*

The positivity assumption was not tested prior to adjustment. However, please see histograms (in Appendix 4: Positivity assumption, illustrating the propensity score distribution, alongside minimum and maximum values in Table 34 (methods used to assess the positivity assumption, as in Schulte *et al.* (2018) (29)), showing that the propensity score is between 0 and 1 in each outcome.

Table 34: Minimum and maximum propensity score values in analysis outcomes

Outcome	**Propensity score range (minimum; maximum)**
Change in HbA1c	0.288; 0.982
Change in triglycerides	0.231; 0.915
Change in ALT	0.298; 0.914
Change in AST	0.307; 0.925
Pancreatitis	0.078; 0.659
Imputed pancreatitis	0.058; 0.671
Mortality	0.057; 0,675
Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; HbA1c, Haemoglobin A1c.	

A29. *From Table 26 on page 138 of the CS, it appears that there are 21 subjects with information about HbA1c at 12 months and 46 with information on TG. Please clarify the sample size of each of the inverse probability weighting (IPW) analysis.*

As shown in Table 26 in the company submission, there are 21 subjects with complete (both baseline and outcome) HbA1c data and 46 subjects with

complete triglyceride data in the GL/PL Natural History study (the SC arm) to use in the ITC. This was not the full sample size of the IPW analyses, as these numbers do not include the subjects in the NIH follow-up study (the treatment arm). Though sample size in the SC arm is low in comparison to the treatment arm, this is due to the nature of the GL/PL Natural History study as described in response to A21.

The sample size for each outcome, separated by study, is presented here for ease of reference in Table 35.

Table 35: Sample size for NIH follow-up study and GL/PL Natural History study

Study type	HbA1c	Triglyc-erides	ALT	AST	Pancreatitis	Mortality
Metreleptin w / wo SC (NIH Follow up study)	101/105 (96.19%)	101/105 (96.19%)	99/105 (94.2%)	99/105 (94.2%)	105/105 (100%)	106/106* (100%)
Supportive care (GL/PL Natural History Study)	21/228 (9.21%)	46/228 (20.17%)	42/228 (18.42%)	38/228 (16.89%)	193/228 (84.64%)	228/228 (100%)

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GL, Generalised lipodystrophy; PL, Partial lipodystrophy; SC, Supportive care; w / wo, with or without.

**106 as one patient who died shortly after metreleptin initiation was included in the analysis*

A30. *Please explain how the stabilized weights in the IPW have been calculated and provide the weight distribution.*

The stabilised inverse probability weights calculated use the marginal probability of treatment instead of 1 in the weight numerator (30) .

Where $P(x)$ is equal to the propensity score:

$$P(x) = P(T = 1 \mid X = x)$$

For treated patients (where $T = 1$), the weight is given by:

$$w = \frac{Pr\,(T = 1)}{P(x)}$$

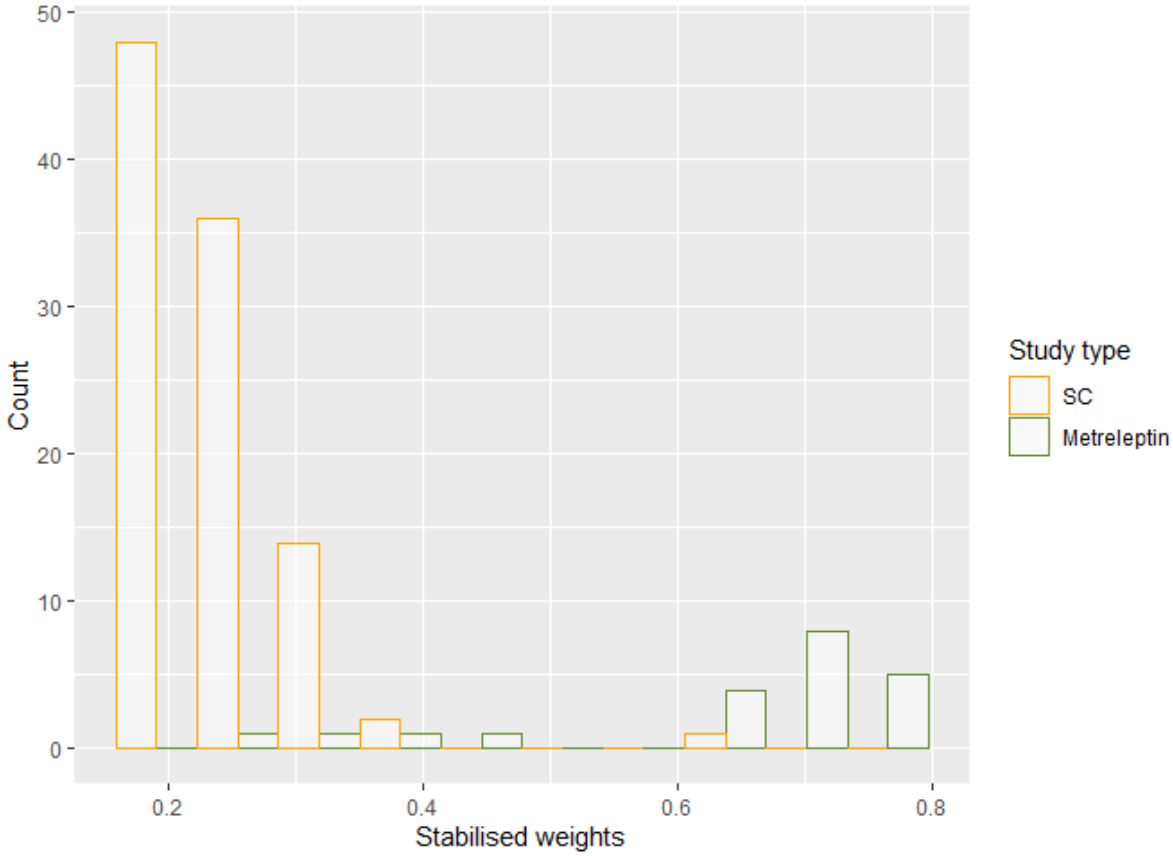
For untreated patients (where $T = 0$), the weight is given by:

$$w = \frac{1 - P(T = 1)}{1 - P(x)}$$

The weight distribution of the stabilised weights is given in

Figure *2*.

Figure 2: Stabilised weight distribution of change in HbA1c outcome



A further sensitivity analysis was also undertaken, exploring the effect of trimming weights at the 1% level as opposed to stabilising, as in Elze *et al.* (2017) (31). The results are given in Table 36 and confirm the robustness of the ITC results in the CS.

Table 36: ATE of metreleptin with or without supportive care versus supportive care alone when trimming weights at the 1% level in HbA1c change from baseline to Month 12

	Coefficient (mean HbA1c, %)	**Robust standard error**	**95% CI**	**p-value**
ATE of metreleptin with or without SC versus SC alone	-1.88	0.32	-2.50, -1.27	**<0.001***
Abbreviations: ATE, average treatment effect; CI, confidence interval; SC, supportive care * denotes significance at the P<0.05 level				

A31. *Please clarify whether the co-primary endpoints are estimated on the same patient population, i.e. change in HbA1C and change of TG are calculated in the same patients.*

The indirect treatment comparison analyses for the co-primary endpoints were performed on the same patient population for the NIH follow-up study. However, there were 25 more patients with complete data available for the change in triglyceride outcome in the GL/PL Natural History study. There were also three patients in the GL/PL Natural History study patient population who had complete data available for change in HbA1c but did not have data available for change in triglycerides.

A32. *Section 9.8.1.1.4 on page 140 of the CS and related tables in Appendix (17.12.5) describe the analysis undertaken for checking the covariate balance before and after weighting. The results suggest that the covariates are almost never balanced (see for example table 108). If, in the sample weighted by the estimated inverse probability of treatment, systematic differences persist between treated and control subjects, this may be an indication that the specification of the propensity score model requires modification. Please comment and also clarify whether the variance, and not only the mean, of the continuous variable(s) is similar between treatment groups in the weighted sample.*

It is correct that covariates remained unbalanced in the specific example referenced. This was thought to be due to the relatively small sample size in the GL/PL Natural History study in the HbA1c outcome. However, the majority of outcomes showed improvement in covariate balance after weighting through all assessments other than the Kolmogorov-Smirnov test – however the applicability of this test in assessing covariate balance is largely disputed, especially in sample sizes less than 1000, (32–34) (for example, please see Table 110, Table 112, Table 114, Table 116, Table 118 and Table 120 of the CS). In all given examples, the variance ratio suggested covariate balance before and after weighting, suggesting the variance of age was similar between treatment groups when weighted.

A33. *On page 137 to 138 of the CS it states: 'Where survival status was unknown at the outcome timepoint, individuals in both studies were censored and presumed to be alive at their last visit date. Therefore, the data set for the mortality outcome could be considered 'complete'. Furthermore, one additional patient who died early for which no laboratory values were available for was added to mortality analyses, in line with the clinical study report (CSR) (55).' Please clarify whether there is information of the patient's status at the last visit date when censored.*

When patient-level data suggested that survival status was unknown, patients were presumed to be alive at the last visit date to an appointment. Though patients were not explicitly recorded as 'alive' at this point, an assumption was made that as survival status was later 'unknown', patients were alive at the point of the last appointment date.

A34. *Figure 47 on page 342 of the CS shows survival until 1-year for the NIH follow-up study and longer FUP for the SC. Please provide number at risk, median and 95%CI. Please also provide the survival curve after PS matching and number at risk, median and 95%CI.*

Please see unweighted (Figure 3) and weighted (Figure 4) survival curves and number at risk. We were not able to obtain 95% CIs for the number at risk using the R **survival** and **survminer** package (**survfit** and **ggsurvplot** function). The median estimated number at risk values are shown in the 'Treatment' section of Figure 3 and Figure 4.

Figure 3: Unweighted survival curve and number at risk

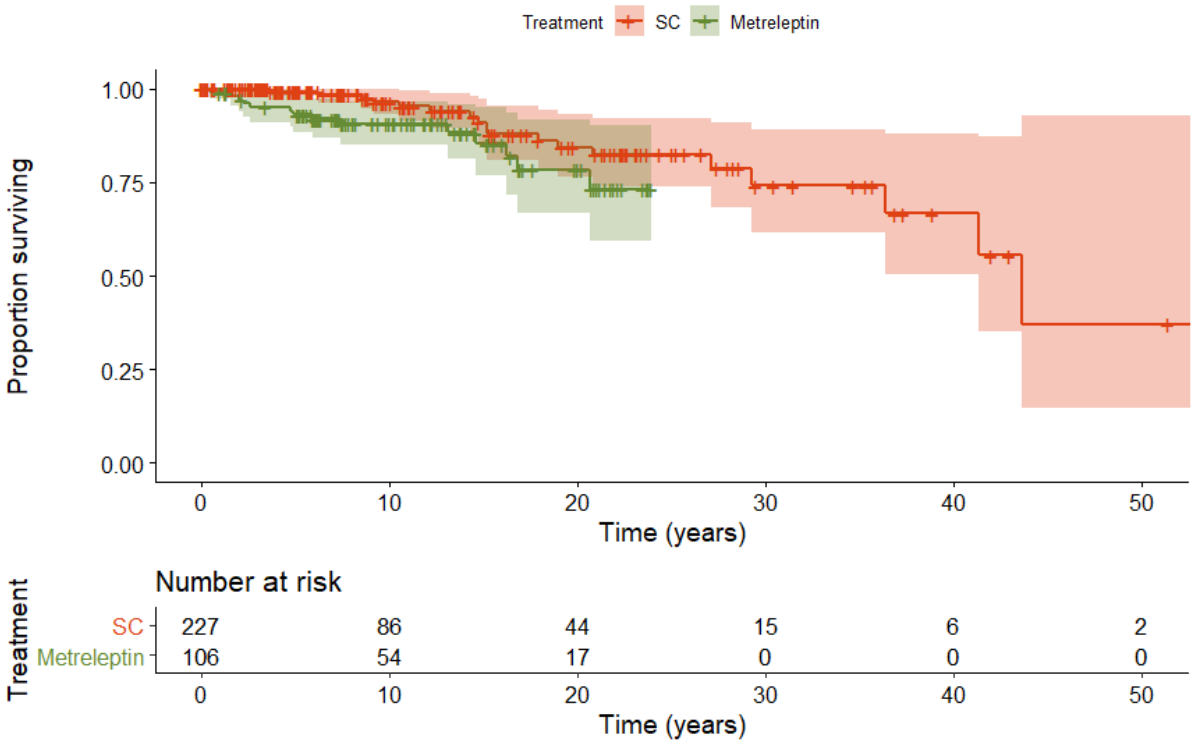
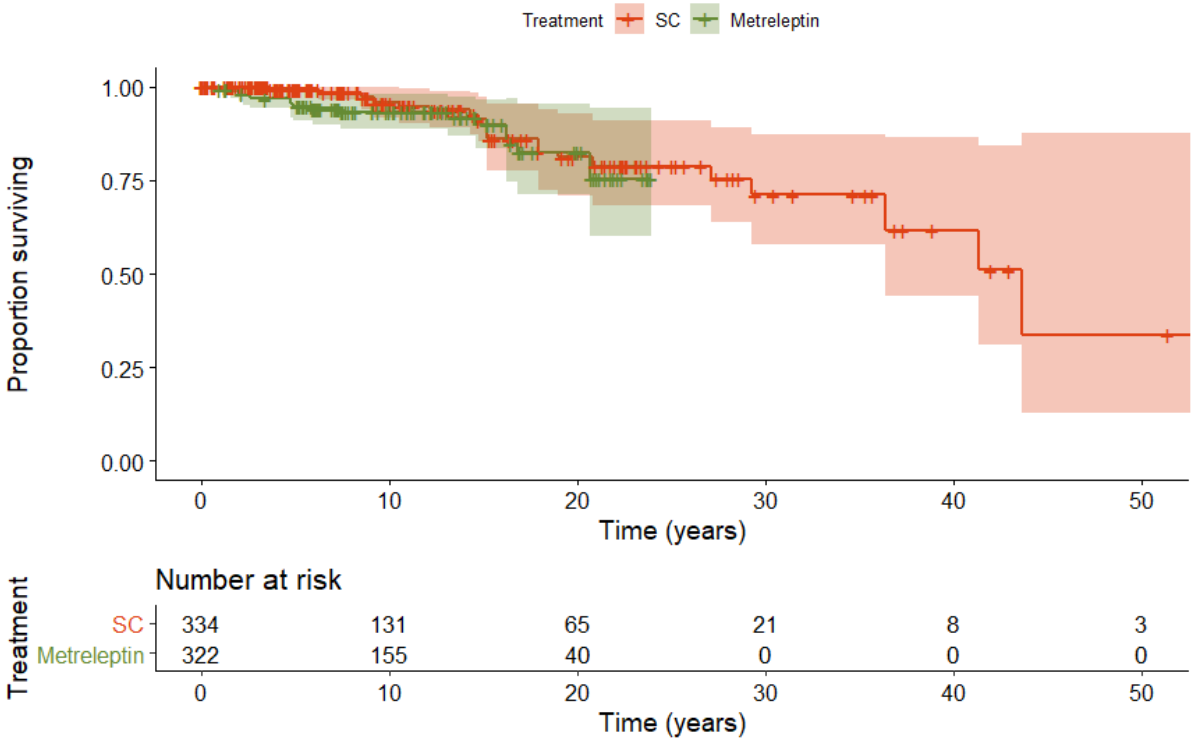


Figure 4: Weighted survival curve and number at risk



A35. *Ethnicity affects absolute levels of HbA1c irrespective of mean blood glucose (2). However in section 17.12.1 it is assumed not to have an effect on the outcome 'assumption, validated by clinicians at Addenbrooke's.' On page 35 of the CS it states: 'In the UK, Addenbrooke's Hospital is the only Reference Centre for Lipodystrophy has registered [redacted] patients with active lipodystrophy [redacted] GL, [redacted] PL).' What is the distribution of ethnicity among these patients? Please validate this assumption with a sensitivity analysis.*

The ethnicity of patients in the Addenbrooke's early access programme (EAP) is described in Table 18 of the CS. Due to the small patient population for which data is available in these analyses, we do not believe it is feasible to carry out a sensitivity analysis incorporating ethnicity into the indirect treatment comparison.

The publication from Cavagnolli et al. provides evidence for individuals without diabetes mellitus that HbA1c values are higher in Blacks, Asians and Latinos when compared to White persons (35). Although small, these disparities might have impact on the use of a sole HbA1c cut-off point to diagnose diabetes mellitus in all ethnic populations. However, the physiological mechanisms underlying these differences, at any glucose concentrations, remain unknown as well as if these differences are clinically relevant. The ethnicity did not modify the association between HbA1c and the risk for cardiovascular disease and final-stage renal disease, and prevalent retinopathy in non-diabetic individuals supporting the same interpretation of HbA1c for the prognosis of diabetic complications among all populations (36). Other factors such as exercise, diet, and other related lifestyle behaviours may affect HbA1c levels, leading to potential for residual confounding, and the bias could have been differential by race/ethnicity.

A36. *Was the ITC performed on all PL patients or only on the PL subgroup of patients with baseline HbA1c>=6.5% and/or TG >=5.65 mmol/L?*

The indirect treatment comparison (ITC) was performed on all PL patients. An assessment was conducted to evaluate the feasibility of conducting a subgroup

analysis for GL, PL overall and PL subgroup populations; however, this is not feasible due to sample size constraints.

A37. *Missing information on pancreatitis was imputed based on the chosen variables for the IPW model. The MICE package assumes that the missing data are Missing at Random (MAR), which means that the probability that a value is missing depends only on the observed value and can be predicted using them. Was this assumption verified?*

As there was no strong reason to believe that data missingness was associated with any identifiable factor or factors, an assumption was made that missingness was random. This was not formally verified.

A38. *On page 135 of the CS the company described how the overlap assumption has been verified. However, in case of multiple covariates it is recommended to inspect the distribution of the propensity score in both treatment groups, which can reveal lack of overlap in the multivariate covariate distributions. Please provide information on if this was investigated and how.*

This was not investigated prior to the analyses. However, the propensity score distribution and range are given in response to A28**.**

A39. *On page 135 of the CS the company stated that 'For categorical covariates (i.e. gender and lipodystrophy type), we assessed whether patients were available in all levels of categories in both study types.' Please provide the results of this analysis.*

The results of the distribution of gender and lipodystrophy type for each outcome are given in, Table 37, Table 38, Table 39, Table 40, Table 41 and Table 42.

Table 37: Distribution of gender and lipodystrophy type in HbA1c outcome

HbA1c		
Lipodystrophy type		
	Generalised lipodystrophy	**Partial lipodystrophy**
Metreleptin w / wo SC	62	39

(NIH Follow up study)		
Supportive care (GL/PL Natural History Study)	3	18
Gender		
	Male	**Female**
Metreleptin w / wo SC (NIH Follow up study)	16	85
Supportive care (GL/PL Natural History Study)	5	16
Abbreviations: w/, with; w/o, without; SC, supportive care; GL, generalised lipodystrophy; PL, partial lipodystrophy		

Table 38: Distribution of gender and lipodystrophy type in triglyceride outcome

Triglycerides		
Lipodystrophy type		
	Generalised lipodystrophy	**Partial lipodystrophy**
Metreleptin w / wo SC (NIH Follow up study)	62	39
Supportive care (GL/PL Natural History Study)	13	33
Gender		
	Male	**Female**
Metreleptin w / wo SC (NIH Follow up study)	16	85
Supportive care (GL/PL Natural History Study)	12	34
Abbreviations: w/, with; w/o, without; SC, supportive care; GL, generalised lipodystrophy; PL, partial lipodystrophy		

Table 39: Distribution of gender and lipodystrophy type in ALT outcome

ALT		
Lipodystrophy type		
	Generalised lipodystrophy	**Partial lipodystrophy**
Metreleptin w / wo SC (NIH Follow up study)	61	38
Supportive care (GL/PL Natural History Study)	10	32
Gender		

	Male	Female
Metreleptin w / wo SC (NIH Follow up study)	16	83
Supportive care (GL/PL Natural History Study)	10	32
Abbreviations: w/, with; w/o, without; SC, supportive care; GL, generalised lipodystrophy; PL, partial lipodystrophy		

Table 40: Distribution of gender and lipodystrophy type in AST outcome

AST		
Lipodystrophy type		
	Generalised lipodystrophy	**Partial lipodystrophy**
Metreleptin w / wo SC (NIH Follow up study)	61	38
Supportive care (GL/PL Natural History Study)	10	28
Gender		
	Male	**Female**
Metreleptin w / wo SC (NIH Follow up study)	16	83
Supportive care (GL/PL Natural History Study)	9	29
Abbreviations: w/, with; w/o, without; SC, supportive care; GL, generalised lipodystrophy; PL, partial lipodystrophy		

Table 41: Distribution of gender and lipodystrophy type in pancreatitis outcome

Pancreatitis		
Lipodystrophy type		
	Generalised lipodystrophy	**Partial lipodystrophy**
Metreleptin w / wo SC (NIH Follow up study)	64	41
Supportive care (GL/PL Natural History Study)	73	120
Gender		
	Male	**Female**
Metreleptin w / wo SC (NIH Follow up study)	16	89
Supportive care (GL/PL Natural History Study)	57	136

Abbreviations: w/, with; w/o, without; SC, supportive care; GL, generalised lipodystrophy; PL, partial lipodystrophy

Table 42: Distribution of gender and lipodystrophy type in mortality outcome

Mortality (total data set)		
Lipodystrophy type		
	Generalised lipodystrophy	**Partial lipodystrophy**
Metreleptin w / wo SC (NIH Follow up study)	65	41
Supportive care (GL/PL Natural History Study)	79	149
Gender		
	Male	**Female**
Metreleptin w / wo SC (NIH Follow up study)	16	90
Supportive care (GL/PL Natural History Study)	68	160
Abbreviations: w/, with; w/o, without; SC, supportive care; GL, generalised lipodystrophy; PL, partial lipodystrophy		

A40. *On page 136 of the CS, it is stated 'As regression-based methods such as multivariate regression make parametric assumptions about the outcome variable, these assumptions were tested and are reported in Section 17.12.2.' Please provide information on whether it was investigated if the distribution of the variables is still not normally distributed after transformation.*

This was not investigated prior to these analyses. However, the results of these analyses are presented in Appendix 5: Transformed outcome distributions). Though transformation did improve skew, normality was not achieved in any outcome.

A41. *Are there any differences in patient characteristics between subjects who received metreleptin with supportive care versus those who received metreleptin without supportive care? Please provide a comparison between these two subgroups.*

For patients in NIH studies 991265/20010769, as noted in Section 9.4.7 Prior and Concomitant Therapy of the CSR, patients were advised by their doctors

as to which permitted concomitant medications were necessary to take in addition to metreleptin. Brown also reports that lipodystrophy patients are refractory to conventional treatments, especially anti-hyperglycaemic agents, resulting in the use of very high insulin doses which are ineffective to achieve adequate diabetes control in many lipodystrophy patients and is simply impractical in a clinical context (3).

As noted in response to A14 and A15, baseline concomitant medications are presented in Table 12 of the CSR. The baseline characteristics for patients who were on concomitant medications at baseline compared those who were not on concomitant medications at baseline in NIH studies 991265/20010769 are presented in Table 43.

Table 43: Baseline characteristics of patients in NIH studies 991265/20010769 by baseline concomitant medication use

	Any baseline concomitant medication (n=94)	No baseline concomitant medication (n=11)
Age at metreleptin initiation, years (mean, SD)	25.7 (14.9)	7.45 (5.2)
Gender, Female (n, %)	82 (87.2%)	7 (63.6%)
Lipodystrophy type, GL (n, %)	53 (56.4%)	11 (100%)
Baseline HbA1c, % (mean, SD)	8.59 (2.2)	6.22 (1.8)
Baseline triglycerides, mg/dL (mean, SD)	1,309.56 (2274.2)	334.18 (201.4)
Abbreviations: HbA1c, Haemoglobin A1c; GL, Generalised lipodystrophy; SD, Standard deviation. [1] Baseline medication defined as a medication with a start date on or before and stop date on or after metreleptin initiation, as flagged in the Veristat dataset. [2] A small portion of patients are missing baseline laboratory values.		

Patients who had no baseline concomitant medications were all GL and were younger than those who were on baseline concomitant medication (7.45 vs. 25.7 years). As such it is reasonable to assume that patients not on baseline concomitant medications are likely to be too young to have developed severe complications associated with lipodystrophy such as uncontrolled diabetes and hypertriglyceridaemia, requiring treatment with these medications (3).

The values in Table 43 support the choice of covariates in the indirect treatment comparison which included covariates for age, gender and lipodystrophy type (GL/PL). As stated in Section 9.8.1.1.2 of the company submission, HbA1c and triglycerides were considered as covariates as part of a sensitivity analysis. However, such a sensitivity analysis not deemed feasible due to the extent of the missing data in the GL/PL Natural History study, alongside the limited number of mortality and pancreatitis events across the studies.

A42. *Please explain whether there is a difference in patients' characteristics between those who discontinued treatment with antidiabetics/lipid lowering and those who did not.*

The baseline characteristics for patients who discontinued all concomitant medications compared with those who did not discontinue concomitant medications all in NIH studies 991265/20010769 are presented in Table 44.

Table 44: Baseline characteristics of patients in NIH studies 991265/20010769 by status of concomitant medication discontinuation

	Any concomitant medications at baseline (n=94)	
	Discontinued all concomitant medications	**Did not discontinue all concomitant medications**
Patients with baseline concomitant medication (n)	26	68
Age at metreleptin initiation, years (mean, SD)	24.58 (15.5)	26.15 (14.8)
Gender, Female (n, %)	21 (80.8%)	61 (89.7%)
Lipodystrophy type, GL (n, %)	20 (76.9%)	33 (48.5%)
Baseline HbA1c, % (mean, SD)	8.82 (2.0)	8.51 (2.3)
Baseline triglycerides, mg/dL (mean, SD)	724.8 (926.0)	1,531.1 (2,581.3)
Abbreviations: HbA1c, Haemoglobin A1c; GL, Generalised lipodystrophy; SD, Standard deviation. [1] The same population was used for the NIH follow-up in the indirect treatment comparison (n=105).		

[2] Baseline medication defined as a medication with a start date on or before and stop date on or after metreleptin initiation, as flagged in the Veristat dataset.
[3] Follow-up medication was defined as prescriptions within ± 45 days of 1-year post-metreleptin initiation.
[4] A small portion of patients are missing baseline laboratory values.

At baseline, comparing patients who discontinued concomitant medications vs. patients who did not, age (24.58 vs. 26.15 years), proportion of females (80.8% vs. 89.7%) and HbA1c (8.82% vs. 8.51%) appear similar. Aligned to the results of the Delphi Panel in Tables 47-48 CS, proportion of GL patients (76.9% vs. 48.5%) appeared higher in those who discontinued all concomitant medications. Baseline triglycerides appear lower in those who discontinued all concomitant medications but owing to the large standard deviations of these values, so no conclusions can be drawn as to their differences.

A43. *HbA1c is not only a useful biomarker of long-term glycaemic control but also a good predictor of lipid profile. Please explain how the company took into account the correlation between these outcomes.*

From a therapeutic perspective, it might not be appropriate to consider the correlation between the HbA1c and triglyceride outcomes. High triglycerides are usually a feature of severe HbA1c imbalance and tend to decrease as metabolic control improves. Naqi et al. showed a correlation between HbA1c and triglyceride level in type 2 diabetes mellitus patients with a HbA1c cut-off value of 7% where 74% patients had high triglycerides and showed a significant association with high triglyceride levels (37). However, recent studies also indicate triglyceride levels as an independent risk factor and predictor for type 2 diabetes mellitus (38). In addition, dyslipidaemia can be also present as a result of familial predisposition. Therefore, HbA1c and triglycerides should be considered as separate for the purpose of treatment goals. In the pathophysiology of lipodystrophies, the lack of subcutaneous adipose tissue leads on the one hand to a deficiency of the adipose tissue hormone leptin and on the other hand to a reduced storage capacity for the fat/energy. As a

consequence of the leptin deficiency and the reduced fat storage capacity, a pronounced hypertriglyceridaemia develops, and ectopic fat deposition occurs in internal organs and muscles. This in turn leads to a pronounced insulin resistance, which in turn increases hypertriglyceridaemia (15). In younger lipodystrophy patients, especially toddlers and children, dyslipidaemia tends to develop before diabetes (25), taking some time for lipotoxicity damage to overcome the functional pancreatic adaptation and develop beta cell dysfunction. HbA1c should be treated as a metabolic risk factor linked to diabetic effects and triglyceride rebound, while triglycerides should be treated both as a metabolic, cardiovascular and pancreatitis risk factor.

Section B: Clarification on cost-effectiveness data

Clinical Inputs

B1. ***Priority Question:*** *Section 12.1 (CS, Table 36, page 168) appears to indicate that data for the GL and PL patients, used in the economic analyses, were taken from NIH 991265/20010769 GL patients and the PL subgroup patients. Please clarify which patient groups, from which studies were used in the economic analysis.*

The mean age of patients and the gender split were obtained from National Institute of Health (NIH) studies 991265/200110769 from the GL patients and PL subgroup. The proportional split of GL and PL patients was informed using Early Access Programme (EAP) data from Addenbrooke's Hospital. As the EAP programme has been running for 10 years in the main centre of care for lipodystrophy, it has been assumed that the split of patients at this centre will be representative of eligible patients in the UK.

B2. Please specify the source for the baseline triglycerides (TG) used in the model (refer to sheet 'Data Store').

Upon reviewing this value, we have concluded that this value is incorrect. As such, the model will be updated to account for revised triglyceride baseline values, drawn from NIH studies 991265/20010769, of 14.5 mmol/L (1283.25 mg/dl) and 14.8 mmol/L (1309.8mg/dl) for GL and PL patients, respectively.

Triglyceride levels are only used in the model as part of the stopping rule. As outlined in the company submission section 10.1.16, the stopping rule has only been applied to PL patients. Therefore, the triglyceride baseline value for GL patients is redundant in the base- case and would only be used in model if the user selected the option to include GL patients in the stopping rule. Further model updates are in progress as part of the 'model functioning' clarification questions. As such, all model updates (including revised baseline triglyceride values) will be presented in the updated model sent by 22nd June 2020.

B3. *On page 67 of the CS it is stated that 'Dietary modification is an essential element in the management of patients with these disorders.' The 3 countries have different diet cultures. Please perform an additional analysis using patients from the NIH centre only from the natural history study. Please provide the option in the model to select between the company's base-case analysis and this analysis based on limited centres.*

We sought further clarification from the ERG with respect to the details of this request, and the further information was provided:

"*Please perform the ITC analysis on the co-primary endpoints for patients treated in the NIH centre only. Additionally, please provide the distribution by country of origin of the patients treated in the NIH centre.*"

91 of the 228 patients used in the indirect treatment comparison in the GL/PL Natural History study were treated at the NIH centre. As summarised in Table 26, page 138, in the company submission, there were limited complete data available in the GL/PL Natural History study for HbA1c and triglycerides due the nature of this study (an observational chart review study). In preparing to conduct this analysis, it was identified that the sample size for this sub-group is reduced too substantially, making it unfeasible to fit a reliable model to the data for this sub-group. Table 45 shows the country of origin of patients who were part of both the NIH and NIH follow-up studies.

Table 45: Country of origin of patients treated in the NIH centre

Country of origin	Number of patients
United States	70
Belgium	2
United Kingdom	2
Madagascar	2
Serbia	1
Spain	2
Canada	4
Turkey	2
India	1
Lithuania	1
Germany	1
Peru	2
Israel	2
Italy	1
Albania	1
Pakistan	1
Argentina	6
Saudi Arabia	2
Unspecified	2

B4. The section of the CS dealing with safety and adverse events includes the following text on page 126:

'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. As noted in the SmPC, 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 rates of premature discontinuation, 26% (excluding the 10 patients who were transfered to another program) for NIH 991265/20010769 and 58% for FHA101 (CS, Tables 19 and 20) and the reported non-compliance rate of 10% for NIH 991265/20010769 (CS, Table 19), please explain/justify why the increased risk of pancreatitis on discontinuation of therapy is not considered in the cost-effectiveness analysis.

The worldwide incidence of acute pancreatitis (AP) per year is 0.005 - 0.08% (39) and approximately 20% will develop a moderate or severe AP with a mortality rate of 13 to 35% (40). It is well known that hypertriglyceridemia (HTG)-associated AP leads to a worse clinical outcome in terms of significantly increased persistent organ failure and significantly increased mortality than AP associated with other causes (41). There is evidence from case reports and clinical trials that lipodystrophy patients have an even higher risk of acute pancreatitis. In the NIH Follow Up study, 52.3% and 30.9% of PL and GL patients respectively reported at least one pancreatitis before the initiation of metreleptin.

The increased risk of pancreatitis due to discontinuation is accounted for in the cost-effectiveness model, through the loss of treatment related pancreatitis risk-reduction upon discontinuation. As the pancreas is one of the six sub-models, and pancreatitis one of the model health states, the increased risk upon treatment discontinuation has been considered. Outside of this risk increase post-treatment (sustained for the patient's remaining lifetime), no

further increase in risk is modelled as any such increase would likely be complex to model, extremely short term, and would likely yield negligible impact on a single annual probability, if at all.

B5. *HbA1c is used as a surrogate outcome to predict transition probabilities in the cardiovascular, kidney, neuropathy and retinopathy sub-models. This seems strange form the cardiovascular events model. Can the company explain why they consider 'the transition probabilities may be an underestimate of the cardiovascular risk for lipodystrophy patients.'*

The Delphi Panel was employed to determine the aetiology for the development of organ-specific complications from a panel of leading experts in lipodystrophy. Consensus was achieved amongst panel experts that the causes of cardiovascular complications in lipodystrophy patients are attributable to:

- Elevated triglycerides
- Elevated HbA1c or comorbid diabetes
- Other lipodystrophy-related cause (outside of the effect of elevated TGs/ HbA1c and other diabetes-related causes)

As described in Section 12.1 of the company submission, the risk of developing cardiovascular complications employed in the cost-effectiveness model was based on the risk of comorbidities reflective of those seen in diabetes patients; and the reduction in the risk of cardiovascular complications for metreleptin-treated patients in the cost-effectiveness model is driven solely by the HbA1c reduction compared to supportive care.

Whilst clinicians agreed that elevated triglycerides are a cause of cardiovascular complications in lipodystrophy patients, it was decided that inflating the risk of cardiovascular events further based on triglyceride levels (in addition to HbA1c-driven risk), would lead to an overestimation of the risk of cardiovascular events due to the correlation between HbA1c and triglyceride levels.

Additionally, clinicians agreed that the risk of cardiovascular events is also attributable to other lipodystrophy-related cause (outside the effect of elevated

TGs or HbA1c). The omission of these aetiologies from the calculation of cardiovascular transition probabilities, leads us to believe that the transition probabilities may underestimate the cardiovascular risk for lipodystrophy patients. The ITC demonstrated that metreleptin significantly reduces triglyceride levels compared to patients treated with SC. As such, the model is expected to underestimate the cardiovascular risk reduction in metreleptin-treated patients.

B6. *Delphi group assumptions are based on 10 clinical experts, 3 of these were UK-based. Can you please provide a UK-specific perspective for Delphi generated inputs – or at least some assessment as to whether the assumptions from the UK differed from those in other countries (Turkey, Italy, Spain, US, Germany) – this will be particularly relevant for resource use estimates where there was considerable variation in mean difference estimates.*

The Delphi Panel survey is a group facilitation technique, which is an iterative multistage process, designed to transform clinical expert opinion into group consensus. As such, provision of UK-specific Delphi generated inputs is not plausible.

Where experts were unable to unanimously agree with the consensus statement, [redacted] chaired a clinical discussion aimed at reaching unanimous agreement. Consensus was set at 80%, meaning that findings from the Delphi Panel could not be used unless at least one of the three UK experts agreed with the consensus statement.

Participants reached consensus that differences between the number of routine monitoring visits for lipodystrophy patients treated with SC alone, compared to those treated with metreleptin, would only be expected in the first 12 months after metreleptin initiation. While all participants agreed that an extra visit or two to an endocrinologist can be expected in the first 12 months during metreleptin initiation, it was apparent during the consensus meeting that inter-country differences existed in the other types of healthcare practitioners who patients are also monitored by. All three UK clinicians stated that visits to an

endocrinologist specialist are typically accompanied by visits to a dietician and a diabetic nurse. Consensus statements were updated in response to this feedback. As the cost-effectiveness model is from the perspective of the NHS and PSS, these UK-specific resource use estimates were highly representative and deemed appropriate to use.

B7. **Priority question**: Please include Grade 3 and 4 TEAEs and their impact on HRQoL and costs in the model.

When reviewing whether to include AEs in our cost-effectiveness model, considerations included:

- the incidence and whether the potential impact on cost-effectiveness could be significant
- whether these adverse effects were likely to be attributable to metreleptin as opposed to symptoms of lipodystrophy progression

Based on Table 24 of the submission (adverse events from NIH studies 991265/20010769), we decided that side effects with <5% incidence would not have a significant impact on the cost-effectiveness (even if it is assumed that these are attributable to metreleptin). Drug-related serious AEs also occurred in <5% of patients (3 GL patients out of 66 and 0 PL subgroup patients out of 31) and were therefore also deemed to impact cost-effectiveness only marginally.

The adverse events in Table 24 of the submission with a ≥5% Incidence overall, that would be considered Grade 3 or Grade 4 TEAEs, are consistent with the expected adverse events associated with lipodystrophy progression. We therefore do not feel it is appropriate for these to be included in the model.

B8. ***Priority question:*** *The CS states that 'Annual discontinuation rate for treatment non-compliance from NIH studies 991265/200110769 (1.50% for patients with GL and 3.86% for patients with PL) were employed in the model. Discontinuations due to all reasons observed in the NIH studies 991265/200110769 were not considered to represent that expected to be observed in clinical practice because a number of patients discontinued the*

studies prematurely to enter the Early Access Programme.' Please provide the annual discontinuation rate due to all reasons for GL and PL patients separately and clarify how many patients discontinued the NIH studies 991265/200110769 studies to enter the Early Access Programme.

The annual discontinuation rates due to all reasons from NIH studies 991265/200110769 are 7.91% and 10.76% for GL and PL patients, respectively. The data used to calculate the annual discontinuation rates are presented in Table 19 of the submission. From the 23 GL patients who discontinued treatment prematurely, 8 of these patients discontinued to transfer to EAPs. From the 15 PL patients who discontinued prematurely, 2 of these patients discontinued to transfer to EAPs.

B9. Priority question: In section 12.2.2 the CS states that '*The clinical benefits observed with metreleptin with respect to HbA1c reduction, liver complications and reduction in the episodes of pancreatitis are sustained in the model while on treatment and partially post discontinuation'.* In Section 9.6.1 the CS states that '*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* (9)*. Mean HbA1c and triglyceride levels through month 48 in GL patients and month 36 in PL subgroup patients are shown in Figure 15 and Figure 16* clarify for how long the model assumes the partial treatment effect post discontinuation, the size of the continued treatment effect assumed for these clinical outcomes and how these assumptions are justified by the long-term data quoted in the CS. Please provide the option in the model to use the durations of 48 and 36 months for the continued treatment effect for GL and PL patients respectively, accounting for the proportion of treatment effect which remains over time.

In patients receiving metreleptin, HbA1c reductions occur as a one-off event at the start of treatment (model start); this decrease does not occur in patients receiving SC alone. From this point, HbA1c begins to rise on an annual basis at the same rate in patients who remain on treatment and who discontinue, as well as those treated with SC alone. This annual rise continues up to a ceiling

value of 12%, based on clinical opinion from the Delphi Panel (16). As such, there is a 'lag' effect on HbA1c with treatment (i.e. a treated patient starts from a lower HbA1c value than if they did not receive treatment); we feel it would be unrealistic to reverse the reduction at a specific point (i.e. to model a 'jump' in HbA1c), given all patients' HbA1c levels rise to the same ceiling point over time.

Liver benefits are maintained post discontinuation under the assumption that a short-term reduction in fatty deposits and accumulation in the liver will yield a longer-term benefit – creating a similarly "lagged" effect and slowing the progression to later stages of disease.

Furthermore, it should be noted that clinical improvements seen in NIH studies 991265/200110769 (9) (and subsequent ITC) upon which the model is based are inclusive of discontinued patients, suggesting any impact this has on the overall benefit of metreleptin has already been factored into the values used.

As requested, we will include an option to remove the effect of liver benefits after 36 and 48 months, as this is feasible to implement under the current structure.

HRQoL

B10. Priority question: In the model 50% of the HRQoL treatment effect is maintained over the patient's and carer's lifetime after treatment discontinuation. What evidence is there to support this specific assumption of continued treatment effect? Please provide the option in the model to amend this assumption (independent of duration of effect (question B9) and clearly signpost this option.

This assumption is implemented as a way of capturing a number of factors. The first is reflecting the "lag" in treatment effect as described in B9, and the longer-term benefits this will entail. Furthermore, while not captured via the organ-specific models except for its inclusion as part of the stopping rule (for reasons outlined in the response to question B5), the ITC has demonstrated a clinically significant reduction in triglyceride levels amongst metreleptin-treated patients; this would also be expected to contribute to the initial and subsequent sustained

effect, and we would expect the same lag as with HbA1c, assuming it were modelled in a similar way. The experts forming the Delphi Panel (16) all agreed that triglycerides contribute to the development of cardiovascular complications in lipodystrophy patients. Therefore, treatment with metreleptin also further reduces the risk of cardiovascular and other complications in a way not captured in the model for reasons of conservatism (to avoid 'doubling' cardiovascular effects by using both markers. As such, even after discontinuation, we feel it is reasonable to expect that a patient would, to some extent maintain some cardiovascular and other treatment related benefit with respect to triglyceride reduction.

Furthermore, per question B9 it should again be noted that clinical improvements seen in NIH studies 991265/200110769 (9) (and subsequent ITC) upon which the model is base are inclusive of discontinued patients, suggesting any impact this has on the overall benefit of metreleptin is already factored into the values used.

B11. Priority question: *In the model sheet 'QoI Inputs' cells C11 and C12 contain utility values for SC and Metreleptin. Could the company please explain the source of these utility values, the quality of life instrument or methods used to elicit the utility values from patients and how they were estimated?*

These values reflect the treatment benefit associated with metreleptin treatment compared to treatment with supportive care alone in terms of HRQoL that have not been captured in the six sub-models. As such, we have applied a difference in utility – a decrement of -0.12 between the metreleptin and supportive care cohorts (the source of this is explained below). It is the difference between these values C11 and C12) that is used in the calculations.

Whilst the value of -0.12 was based on a decrement of -0.11 for hyperphagia from the previous metreleptin NICE submission (42), a number of relevant factors were considered in arriving at this value. Whilst this decrement of -0.11 was later revised to -0.071 through reanalysis as part of the previous submission materials (ECD Response, Part B, November 2018) (43), this value

may underestimate the impact of hyperphagia as the DCE cannot fully encompass the patient experience of such a unique aspect of the disease (e.g. members of the general public may not have understood how hyperphagia differs from usual “hunger”).

Bridges *et al.* (44) estimate that hyperphagia is associated with a utility decrement of -0.13 and -0.09 when assessed using visual analogue scale (VAS) and time-trade off (TTO), respectively, among patients with Prader-Willi syndrome. While Prader-Willi syndrome is fundamentally different to lipodystrophy, testimony by lipodystrophy patients on the burden of hyperphagia (section 7.1.1.2 of submission) highlight some similarities between the two conditions along this dimension.

Further to hyperphagia, a number of symptoms associated with lipodystrophy, which metreleptin has been shown to improve (Table 46), have not been captured through the six sub-models due to insufficient data. The decrement of -0.12 also seeks to account for the reduction in the frequency or severity in these symptoms as a result of metreleptin treatment. Our approach has been to remain conservative, as the value used remains within the range of feasible values for hyperphagia alone; if data were available to provide individual decrements relating to all model symptoms listed in Table 46, it is possible that the compounding effect of these multiple symptoms would provide a larger decrement.

Table 46: Lipodystrophy symptom prevalence pre-treatment and improvement post-treatment

	GL Pre-treatment prevalence	GL post-treatment improvement	PL Pre-treatment prevalence	PL post-treatment improvement
Inability to perform work/schoolwork	57.4%	79.5%	20.5%	55.6%
Disruption to female reproductive functioning (PCOS)	41.2%	57.1%	57.1%	33.3%
Hyperphagia	82.3%	100%	71.9%	95.6%
Impaired physical appearance	82.4%	67.9%	68.2%	46.7%

PCOS, Polycystic ovary syndrome

Prevalence data is obtained from patients enrolled in the NIH Follow-up study (10). Data on pre-treatment impairment was collected at enrolment, but prior to trial initiations; post-treatment impairment data was collected one year after metreleptin initiation (see Leptin Replacement Therapy Follow-Up study (NIH Follow-Up study)) and represents the percentage of patients, out of those who displayed pre-treatment impairment, whose symptoms have improved post-treatment.

B12. Priority question: *Table 38 of the Submission states that it is assumed that each patient has 2 carers according to Lipodystrophy Caregiver Survey. The caregiver survey included 9 carers, of which 4 stated they were the only carer, 4 stated there were 2 carers and 1 stated 3 carers. Both the average carer and multi carer scenarios in the model have a value of 2. Please explain the intended difference between the multi and average carer scenarios and correct the average carer approach to reflect the data average (mean) from the carer survey.*

The multi carer scenario in the model became redundant upon using a rounded average carer value of 2, as it is most representative of the most common scenario in practice. The mean number of carers from the caregiver survey was 1.67.

B13. *The company submission states that one of the key drug-related complications identified was hypoglycaemia. However, this was assumed to have a minimal impact on HRQoL given the short duration of symptoms. Please provide evidence for the lack of impact of hypoglycaemia on HRQoL.*

As stated in the company submission in section 9.7.2, the most commonly reported drug-related treatment emergent adverse events (TEAEs) in GL and PL patients from the NIH studies 991265/200110769 included hypoglycaemia (9). None of the cases reported were severe. This adverse effect is consistent with the expected pharmacologic effects of metreleptin.

Hypoglycaemia is where the blood glucose levels drops too low and is very common in patients with diabetes, especially those on insulin. Current supportive care for lipodystrophy patients includes very high doses of insulin (3), putting patients at high risk of hypoglycaemia. Current supportive care for lipodystrophy patients includes very high doses of insulin (3), putting patients at high risk of hypoglycaemia.

Mild to moderate hypoglycaemia is a short, transient adverse effect, which is commonly self-treated and the NHS advises patients to have a sugary drink or snack, test their blood sugar after 10 to 15 minutes after symptoms and treat again with a sugary drink or snack or to eat their main meals (45). Published evidence has shown that the HRQoL impact of mild to moderate hypoglycaemia in patients with diabetes is low. A study by Currie *et al.* (2006) reported utility decrements, which were applied in the cost-effectiveness modelling used in the NICE Clinical Guideline for Type 2 diabetes, NG28, where a utility decrement of -0.014 was applied for a symptomatic hypoglycaemic episode (46). As such, the impact of mild to moderate hypoglycaemic events on HRQoL is minimal.

B14. *Table 35 of the company submission states that 'other symptoms' were assumed to be associated with a utility decrement of 0.22. Please list which other symptoms this was used for in the model.*

Please see the response to Question B11 where a further explanation of the utility decrement applied to supportive care-treated patients. Unfortunately, the 0.22 decrement mentioned in the submission is a typographical error – this value does not feature in the model. The correct decrement of -0.12 mentioned in question B11 seeks to capture the difference in QoL between metreleptin-treated and supportive care-treated patients related to lipodystrophy symptoms outside of the six sub-models.

B15. *Please provide the mean (SE) EQ-5D-3L utility value obtained from carers in the Lipodystrophy Caregiver Burden Survey*.

The mean (SE) EQ-5D-3L utility value obtained from carers has been calculated from the individual respondents data in the *Lipodystrophy Caregiver Disease Burden Survey* is 0.8124 (0.043) (47). This value was obtained using the UK value set generated using the time-trade off valuation technique (48).

B16. Priority question: *In the model utilities for metreleptin are set at 0.81 with a comment 'minus decrement for hyperphagia' – what is this decrement and where/how has it been applied? On page 151 the CS states: 'hyperphagia, a state of hunger likened to starvation is also detrimental to quality of life with an estimated utility decrement of -0.11' whereas on page*

156 it states 'a disutility of 0.13, drawn from the previous metreleptin submission for hyperphagia alone (111) was applied to patients treated by SC alone.' Why the discrepancy on values? Please clarify how the impact of hyperphagia on QoL is accounted for in the model?

Please refer to the response to question B11 for an explanation of how the impact of hyperphagia is accounted for in the model through the decrement applied to supportive care-treated patients.

Costs and Resource use

B17. *Please explain what proportion of drug costs pertains to drug administration costs (i.e. the costs of home delivery and self-administration training, for which it is stated that these will be funded by the company at no additional cost to the NHS).*

Given that the costs of home delivery and self-administration training costs will be funded by Amryt Pharmaceuticals DAC, these have not been included in the drug costs. Therefore, in the model, 0% of drug costs pertains to drug administration costs.

B18. Priority question: Page 200 of the CS, explaining the metreleptin drug costs states: '*These data dose was adjusted for potential future increase in dose if such an increase was seen likely in the future*'. This sentence seems incomplete and its meaning overall is unclear. Please provide a clear explanation of how drug costs were implemented in the model, including the rationale for the titration phase and any subsequent dose adjustments, and how this relates to any empirical data and expert opinions, using complete and grammatically correct sentences.

The long-term dose of each patient per simulation is based on the proportional spilt of patients from the EAP receiving one of three available vials (each with a different dose of metreleptin) for their daily dose (Table 47).

Table 47: Summary of the (proportion) of EAP patients receiving each metreleptin vial size

	11.3 mg vial (10 mg dose)	5.8 mg vial (5 mg dose)	3 mg vial (2.5 mg dose)
Proportion of EAP patients receiving each vial size	13.0%	60.9%	26.1%
Abbreviations: EAP, Expanded access programme; mg, Milligram; n, Number			

This data from the EAP at Addenbrooke's hospital has been probabilistically employed in this patient level model using a Beta distribution to determine the long-term dose received by each patient. Following the titration phase, each patient remains on this long-term dose until discontinuation. As part of the two-cycle titration phase, patients receive the 2.5mg dose for the first cycle and a 5mg dose for the second cycle (with the exception of patients whose long-term dose is 2.5mg).

A titration phase was included to account for the fact that 19 out of the 23 patients whose dose was used to inform the proportions in Table 47 above, have been on metreleptin for at least 2 years. As such, we would expect that a number of these patients are likely to have started on a lower dose and have been uptitrated to the dose accounted for in the table above. This is further supported by the fact that the 4 patients who have been on metreleptin for less than 2 years, are all receiving the 3mg vial (2.5mg dose or less).

B19. *Page 203 of the CS refers to Appendix 13 at two instances. Please make clear, using proper cross-referencing at relevant places, to which of each of the 12 tables in Appendix 13 the company is referring in the text (i.e. using additional references to specific tables in Appendix 13 where needed), to facilitate a clear explanation of how drug costs were exactly implemented.*

The following extract from the submission in Section 12, in which Appendix 13 has been mentioned, has been amended to specify the tables that are being referred to (please note reference citation numbers are as per the original company submission).

The specific medication, form and strength of the medications included in supportive care medications was determined using NHS prescription cost data, 2018 (143), as shown in Appendix 13 in Table 124 and Table 125. NHS prescription cost data were used to identify the most commonly prescribed medication in each of the medication classes listed above. Furthermore, the strength of the most commonly prescribed medication was assumed to be the daily dose (given this falls within the dose recommended in the BNF (144)). For example, the most commonly prescribed HMG CoA Reductase Inhibitor is atorvastatin 20mg tablets. The BNF recommended dose for atorvastatin is 10–80 mg daily and so it was assumed that the dose of atorvastatin for patients is 20 mg daily. In the case that the strength of the most commonly prescribed medication falls outside the BNF recommended dose, it was assumed that the dose was equal to the starting dose. The dose of insulin (number of units per day) was informed using baseline data from the NIH studies 991265/20010769 (17), as reported by Diker-Cohen et al. (74) .The annual cost based on the proportion of patients in each of the subgroups (generalised lipodystrophy or partial lipodystrophy) prescribed each of these medications was then calculated using the NHS drug tariff costs (145). A breakdown of the daily costs per supportive care medication is shown in Appendix 13. Specifically, in Table 126 for patients receiving supportive care treatment alone, and in Table 131 for patients receiving metreleptin with supportive care treatment.

B20. *Page 203 of the CS states: 'In the case that the strength of the most commonly prescribed medication falls outside the BNF recommended dose, it was assumed that the dose was equal to the starting dose.' Please explain what is meant with 'starting dose' in this sentence.*

The dose for the medications used to calculate supportive care treatment costs fell within the BNF recommended dose for all but one medicine. For colesevelam, the dose fell outside the BNF recommended dose.

Whilst colesevelam is also indicated for the treatment of bile acid malabsorption, the recommended dose for this indication was not considered as this indication was deemed irrelevant for lipodystrophy patients. Therefore, two remaining doses were stated in the BNF for:

- Primary hypercholesterolaemia as an adjunctive to dietary measures (monotherapy): 3.75g daily in 1-2 divided doses
- Primary hypercholesterolaemia as an adjunct to dietary measures (in combination with a statin); Primary and familial hypercholesterolaemia (in combination with ezetimibe, either with or without a statin): 2.5 - 3.75g daily in 1-2 divided doses.

In reference to these doses, the starting dose refers to the lower end of the recommended dosing range. Therefore, a dose of 2.5g daily was used in the calculations for supportive care medication costs. Whilst 3.75g daily could also be considered the starting dose, 2.5g daily was chosen as a conservative assumption.

B21. Priority question: *Please explain how the company has concluded that the impact of adverse events on costs is minimal, as part of a justification for not taking these costs into account.*

Most adverse events observed in the NIH follow-Up study were consistent with the expected adverse events associated with lipodystrophy progression (43). Therefore, it is expected that these adverse events can be managed as part of the normal clinical practice for patients with this complex condition. As such, the type and incidence of adverse events are assumed to be similar between patients treated with metreleptin and those treated with supportive care alone.

As stated in section 9.7.2.1 of the company submission, drug-related serious adverse events (SAEs) were not common in NIH studies 991265/20010769, reported in only 3 (4.5%) GL patients and in none of the PL subgroup patients. Due to the low frequency of drug-related SAEs, it has been deemed that the inclusion of these adverse event treatment costs in the model would have minimal impact.

The approach of not taking adverse event costs related to metreleptin into account as they are deemed to have minimum impact on the cost-effectiveness, is also consistent with approach used for the comparator arm. As demonstrated by clinical expert opinion from the Delphi Panel process (16), patients treated with metreleptin can expect a reduction in supportive care medications used to

manage metabolic abnormalities. The expected reduction in such medications, would of course result in a reduced incidence of adverse effects associated with supportive care medication for metreleptin-treated patients. However, as mentioned above, supportive care adverse event costs have also not been included in the model for consistency.

B22. *The text of the CS distinguishes between the costs of 'supportive care alone' and 'metreleptin with supportive care costs', whereas the model distinguishes between the costs of 'supportive care alone' and 'metreleptin with or without supportive care costs'. Please clarify whether explanations, terminology and numbers that are provided in the text of the CS should be followed, or those in the model.*

All patients within the model, including metreleptin-treated patients, accrue costs for supportive care treatment. Therefore, 'metreleptin with supportive care costs' is the appropriate terminology – 'metreleptin without supportive care costs' will be replaced with this term. The sub-section 'metreleptin with supportive care costs' in section 12.3.6 of the submission accurately represents the methodology used in the model to generate the supportive care medication costs for metreleptin-treated patients, despite this difference in terminology.

B23. *On page 72 it is stated that 'Cosmetic treatment may be required to improve physical appearance, however patients in England may have problems gaining funding for such procedures through the NHS and they may need to seek private treatment which can present a personal financial burden. Anti-androgens may be required for PCOS and hyperandrogenism. Other services that may be required include referral to a dermatologist for severe acanthosis nigricans and/or skin tags and referral to fertility services'. Can the company confirm that the experiences of those from available evidence on metreleptin were equivalent to those on comparator and that all associated costs and utilities have been adequately and appropriately accounted for.*

The lack of evidence surrounding cosmetic surgery as a response to psychological distress and physical discomfort some lipodystrophy patients may experience is echoed throughout international lipodystrophy guidelines

(5,49) and therefore experiences of patients on metreleptin and its comparators is not available.

Although metreleptin replacement therapy was shown to improve metabolic alterations in lipodystrophic syndromes, patients' adherence and satisfaction with treatment have never been evaluated.

However, there is preliminary evidence available from the EAP in France which found that changes in appearance were visible in some female PL patients who had been treated with metreleptin for at least 12 months. It should be noted that improvement in physical appearance has not been clinically confirmed, would not alter the metabolic state of the patient and is not a feature of the drug's indication (50).

Plastic surgery (breast implants, dermal fillers, lipectomy, or liposuction) and psychological support can improve the well-being of some patients (51). However, in a mouse model of acquired generalized lipodystrophy established by surgical removal of multiple fat depots, including subcutaneous fat in the inguinal, exacerbation of the metabolic disorders was observed (52).

B24. Priority question: *In the CS it is stated on page 208 (information presumably copied from Appendix N of the NICE NAFLD guideline; p. 618 – 619) that liver transplant costs '…were sourced from Brown et al. and Wright et al. (152, 153)'. Reference152 refers to the HTA report by Wright et al. (which indeed lists the liver transplant costs on page 48) but reference 153 is listed as Brown et al., but which seems to actually be (based on the title and journal) 'Belfort, R., Harrison, S. A., Brown, K., Darland, C., Finch, J., Hardies, J., ... & Berria, R. (2006). A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. New England Journal of Medicine, 355(22), 2297-2307' instead. However, this paper does not report cost information. The ERG assumed that the correct reference (both for the CS as well as Appendix N of the NAFLD guideline) for this cost information is 'Dakin, H., Bentley, A., & Dusheiko, G. (2010). Cost–utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value in Health, 13(8), 922-933'. Although the costs for liver transplant in the CS are in line with these (ERG assumed)*

sources for the first year, this is not the case for the costs of liver transplant from the second year onwards (both in the CS as well as Appendix N of the NAFLD guideline). Furthermore, a substantial component of the costs as mentioned in Dakin et al. apply to the costs for treatment with hepatitis B immunoglobulin to prevent recurrence of hepatitis B. It is not clear to the ERG whether these costs are also applicable in the current context.

a) *Please check that the correct references are provided in relation to the costs of liver transplants (including checking that references copied from other sources are correct).*
b) *Please check that the assumptions regarding liver transplant costs in all years are in line with the information provided in the correct sources (i.e. not merely copied from Appendix N of the NAFLD guideline).*
c) *Please confirm whether the costs for treatment with hepatitis B immunoglobulin are included in the liver transplant costs that are used in the model, and either provide justification for this choice if it is considered as correct or amend the analysis to exclude these costs if it is considered as incorrect.*

As highlighted, the sources of liver costs and references were obtained directly from the NICE NAFLD guidelines, which had been developed by the Guideline Development Group consisting of UK clinical experts (53). Upon reviewing, these references further, we believe the correct reference instead of Brown *et al.* (54) is Dakin *et al.* (55). As outlined in section 6.1.3.2 of the submission, clinical experts have highlighted that the liver disease complications observed in lipodystrophy are analogous to that associated with non-alcoholic fatty liver disease (NAFLD). As such, it can be expected that the costs associated with a liver transplant in the NICE NAFLD guidelines are applicable to lipodystrophy patients. We therefore followed a previous NICE validated approach that had been used and accepted in these guidelines, and believed their assumptions were correct and therefore, the costs appropriate (53).

B25. Priority question: *Please explain whether the cost for ESRD that is used in the model is based on a specific age group (or a weighted average, or otherwise), and provide justification for this choice.*

The cost of the ESRD health state cost was informed using the 'CKD stage 5' cost from the evidence base which formed the NICECG182 (56), which in turn were taken from NICE CG73 (57). NICE CG73 has now been withdrawn from the NICE website (replaced with NICE CG182) and we are unable to determine whether the cost for 'CKD stage 5' is based on a specific age group. However, it is stated within the NICE guideline CG182 that the CKD costs included inpatient stays, nephrology outpatient visits, antihypertensive drugs, and GP visits. We have assumed that, at the stage of ESRD, where CKD "has progressed so far that renal replacement therapy (regular dialysis treatment or kidney transplantation) may be required to maintain life" (56) , the costs listed above associated with CKD stage 5 would be accrued independent of age.

Model Functioning

B26. Priority Question: *The model is very time consuming to run. Please remove all analyses separated by gender as these are not subgroups on which NICE can separate decision making and therefore they are not useful, but slow down run time.*

We agree that is not relevant for NICE to issue advice based on gender sub-groups due to equality issues. We have included an option on the 'Results' tab to run cohorts including both genders and provided results for an additional subgroup analysis using the new method provided.

However, the cost-effectiveness model is a patient model and runs analyses based on the gender of patients, which captures and reflects differences in the baseline characteristics between males and females with lipodystrophy. Furthermore, the approach we have used (running separate cohorts by gender and lipodystrophy type) allows for greater interrogation of the population splits without having to re-run analyses. For example, ICERs can be instantly generated for a population with a different proportion of females and males, and

GL and PL patients, by simply amending these inputs; the base-case and overall incremental cost-effectiveness ratio (ICER) produced by the model are weighted by the different sub-groups to produce a weighted ICER that can be used for decision making. It should be noted also that using our approach avoids introducing uncertainty into the ICER for individual genders by removing the impact of small numbers of patients in specific gender subgroups (for example, males with PL making up a small proportion of the overall PL population) by running each gender for the same number of patients. Furthermore, running cohorts irrespective of gender effectively halves the total number of patient runs to generate the cohort.

Computational burden is an inherent trade-off for the benefits yielded by the type of modelling approach we have used. Firstly, the patient level-approach allows better and more accurate representation of the multi-organ involvement of lipodystrophy, and indeed it was the explicit recommendation of the Committee during the previous process which directed us toward models of this nature within diabetes and other relevant conditions. Secondly, by striving to ensure as much of the model engine is provided in an accessible and transparent formats within Excel worksheets, we have sought to provide a model which does not become a black box, as would be the case with calculations housed within Visual Basic for Applications. The latter would give a somewhat faster run time but would be far less easy to interrogate and interpret.

B 27. Priority question: *The model is not very transparent. Please provide the following:*

a. *A document that clearly describes what the function is of each work sheet, including an explanation of formulae used, and of each macro that is in the model.*

b. *A sheet in the model with model settings, allowing all relevant settings of the model to be changed using drop-down menus in this sheet (including an indication of what each setting refers to).*

c. *A separate results sheet in which it is clear whether results are for one cohort or probabilistic cohort results.*

To support the ERG's understanding of the functionality of the model, a teleconference has been held by the modelling team that built to model to explain the layout and the functionality of the model. To support this further, the information has been provided below that explains the function of each worksheet. The macros used in the model have been updated with additional notes within the macros for added clarity.

Introduction sheet

The introduction sheet serves to provide an overview of the model structure and provides model navigation instructions.

QoL inputs sheet

This sheet provides health state decrements for each of the model health states, categorised by each of the sub-models. The sources of the utility decrement values are provided, along with 95% confidence intervals or standard errors where available. Please note the cardiomyopathy health state has been highlighted in grey, as this health state is redundant in the model. The baseline age-dependent baseline utility values employed in the model are also provided on this sheet.

Cost inputs sheet

This sheet provides the dose mix from the EAP used to inform metreleptin costs in the model, as well as the price of each of the available vial sizes (list price and price with PAS). Please see the response to question B18 for an explanation of how these costs are employed in the model. Supportive care medication costs and disease management costs are also included in this sheet, separated by patients treated with supportive care alone and those treated with metreleptin. The health state costs associated with each of the model health states are also displayed, categorised by each of the sub-models. The sources of the health state cost values, along with calculations used to arrive at these costs have been provided. Please note the cardiomyopathy health state has been highlighted in grey, as this health state is redundant in the model.

Model engine sheet

The model engine sheet displays the transition matrices for the cardiovascular, liver, kidney, retinopathy, and neuropathy sub-models. The cardiovascular, kidney, retinopathy and neuropathy sub-model transitions probabilities vary cycle to cycle, depending on the HbA1c level, as further explained in section 12.2.1 of the company submission. Separate transition matrices are presented for the liver sub-model for metreleptin-treated and supportive care-treated patients. The model allows the option for the Delphi Panel-derived (16) risk reduction or the risk reduction based on the Hossain et al. (58) risk equation to be applied to metreleptin-treated patients. The pancreas sub-model is driven solely on the treatment status of the patient. As such, the probability of pancreatitis for supportive care-treated and metreleptin-treated patients are shown.

The markov trace (cells U78:CY181) is categorised by each of the sub-models. The column labelled ‘RNG’ in each of the sub-models, displays the random numbers used to determine the health state within each of the sub-models in which the patient resides for each cycle. The column immediately to the right of the column labelled ‘RNG’, labelled ‘state’ within each of the sub-models, represents the health state in which the patient resides, with ‘1’, representing the least severe health state for each of the sub-models. For example, the

cardiovascular sub-model comprises the following 7 health states (listed in the same order as that in the transition matrix): no cardiovascular disease, angina, myocardial infarction, post-myocardial infarction, cardiomyopathy, stroke and post-stroke. A value of '1' in the 'state' column shows that the patient resides in the no cardiovascular disease health state, a value of '2', in the angina health state, a value of '3' in the myocardial infarction health state, etc. The column labelled 'current' shows whether or not the patient resides in that particular health state within each of the sub-models. A value of '1', demonstrates that the patient resides in that particular health state, with a value of '0' demonstrating the contrary. The columns to the right of the markov trace pertain to the calculation of mortality risk for each cycle. The base-case analysis inflates general mortality by the single highest mortality risk from health states in which the patient resides during each cycle.

The metreleptin cost and disease management costs, per cycle, are shown in cells G191:H291. The supportive care medication costs, per cycle, are shown in cells J191:K291. Cells Z185:CY186 represent the annual health state costs for each of the health states in the markov trace. Cells X191:CY291, 'mirror' the markov trace and displays the health state costs accrued during each cycle, with a clear visual of the health states from which costs are accrued. The total health state cost accrued per cycle is displayed in cells DB191:DB291. The discounted health state costs (event costs) and drug costs are then displayed in cells DG191:DH291.

The same approach has been employed to display the disutility incurred per cycle, whereby cells X298:CY298 'mirror' the markov trace, with a clear visual of the health states from which QoL disutility occurred. The caregiver disutility applied per cycle is displayed in cells M298:M398. Please note that cells X295:CY296 provide the option to display additional caregiver disutilities associated with each of the health states, however these have not been used as part of the base-case. The disutility applied per cycle to patients treated with supportive care treatment alone (outlined in the response to question B11), is displayed in cells J298:J398. The patient's QoL utility per cycle (incorporating

the baseline QoL utility value and applied disutilities) is displayed in cells DB298:DB398 (discounted in cells DG298:DG398).

Sim sheet

Cells B22:W1021 (assuming 1,000 patients per cohort) represent the results of the last cohort of patients to have run through the model. The average results for the cohort are displayed in cells B20:X20. These results are used to inform the 'Cohort ICER' results displayed in cells AA16:AZ16. Please see the response to question B29 for an explanation of the 'Average ICER', 'Overall ICER' and 'Adjusted ICER'. The cells in column BB onwards display the calculations used to derive the mortality curves.

Results sheet

The results sheet has been added to show the overall results for the CEM population. Additional options including dropdown menus have been provided as requested.

OWSA sheet

The OWSA sheet displays all parameters that were included as part of the one-way sensitivity analyses. The user is able to choose the number of cohorts and the number of patients per cohort used in the analysis by altering the values in cell H9 and cell H8, respectively. The OWSA diagram shows the top 10 most influential parameters.

PSA sheet

The PSA sheet serves to generate the cost-effectiveness scatter plot. The user is able to choose the number of number of cohorts and the number of patients used in the analysis by altering the values in cell V5 and cell V4, respectively.

CEAC

The CEAC sheet serves to generate the cost-effectiveness acceptability curve. The user is able to choose the number of number of cohorts and the number of

patients used in the analysis by altering the values in cell S13 and cell S12, respectively.

Mort curves sheet

The mortality curves sheet displays graphs that show the proportion of patients alive at time points from the start of the model for 4 patient subgroups: males with GL, males with PL, females with GL and females with GL.

Model parameters sheet

The model parameters sheet lists parameters used in the model including base case, OWSA, and PSA values.

Data store sheet

The data store sheet displays the data and calculations that have been used to generate inputs for the model.

Inflation sheet

The inflation sheet displays the inflation indices that have been used to inflate costs from previous years.

Rand numbers sheet

The random numbers sheet generates all random numbers used in the model-both freely varying, and fixed random variable seeds (sets of random numbers to generate identical results across cohorts). This option is used to remove uncertainty for validation purposes, and to fix baseline ICERs for use in the one-way sensitivity analysis function.

***B28. Priority question**: In the model it appears that first and second order stochasticity are not clearly separated.*

a. *In the Model Engine, various variables are sampled for an individual patient (age, weight, baseline HbA1C, baseline triglyceride) from a distribution based on the mean and SE (second order uncertainty) from*

the clinical data, rather than from the mean and SD (first order uncertainty). Also, correlations between these 4 and possibly other patient characteristics are not incorporated, despite the fact that these correlations are very likely to exist.
Please correct the instances where distributions should be based on the SD, and please include the observed correlations between these variables, or justify why these correlations have not been taken into account.

b. *Also, please explain when running multiple cohorts, as presented on the Sim worksheet, are we running multiple cohort including only first order uncertainty? And are the cohorts mentioned on the PSA worksheet including second order uncertainty from cohort to cohort?*
c. *What we would expect with a patient-level simulation is that for example the input variable no CVD_ANG has one single value for all patients in a cohort, and also when multiple cohort are run. And that in the PSA, the value of no CVD_ANG is then varied based on its mean and the SE. Please explain if this is currently happening in the model. If so, please explain where we can see that. It is not, please revise the model such that there is a clear separation of first and second uncertainty.*

a. We acknowledge the need to correct the approach to reflect individual- rather than population-level variability, and to reflect correlation between baseline patient characteristics. As such, we have updated the way patient's age, weight, baseline HbA1c and baseline Triglyceride levels are sampled.

   Covariance Matrices have been generated using log-transformed baseline age, body weight, HbA1c and Triglyceride values for GL and PL patients; log transformation was necessary to address skewed data and lack of a normal distribution, especially with respect to triglyceride levels in which a lower bound of zero was offset against some extremely high values. Subsequently a Cholesky decomposition approach has been deployed to allow random sampling of these four

variables (by generating a random z-value from a normal distribution with mean 0 and standard deviation of 1). The generated random samples account for covariance and are then exponentiated to provide randomly sampled values on the correct scale.

It should be noted that due to small patient numbers, possibly further impacted by the aforementioned extreme data points, the variance levels yielded are considerably large, which leads to possibly a greater than expected level of variability than might be realistic. For example, on occasion random samples of age yield higher than realistic values very occasionally and in particular with starting age. As such a formula has been included when this occurs such that a value falling outside the minimum or maximum reported value for the respective subsets GL and PL patients is replaced with that maximum/minimum value as a "cap". While this approach has limitations, it does serve as a means of producing a suitable level of variability from patient to patient (compared to the previous approach), using reported covariance as is feasible, but also addressing the issue of high variance due to small patient numbers.

As a result of these changes, coupled with changes to values including baseline Triglyceride levels, we noted that the proportion of PL patients 'stopping' treatment when running base-case analyses fell to a level outside the expected threshold indicated as expected in discussion with clinical experts at Addenbrookes (expected to be around 25% to 50%). To correct this reduction, an option to include an additional proportion of patients stopping treatment has been included and used in the base-case analysis (this is found in the stopping rule options in the Engine Sheet). The impact of this is to bring the total proportion of PL patients stopping back in line with expected proportions using an assumed 10% increase (yielding stopping rates of approximately 20%, thus remaining conservative).

Cost-effectiveness analysis results have been updated and are shown at the end of the responses. We note that results using this new variability as implemented do not differ significantly from the previous base case, suggesting the model remains robust with this higher level of individual patient variation, and the impact of covariance on patient baseline values. Furthermore, one way and probabilistic sensitivity analysis echo the robustness of model results.

b. When running any analysis, patient characteristics and reductions are sampled randomly for each patient. The individual transitions probabilities, risk of mortality, discontinuation and so forth (detailed in the 'Model Engine' worksheet) are also randomly sampled in all analyses, meaning each patient's pathway through the model is randomly generated. Other variables and parameters are fixed, unless a probabilistic analysis is run, in which case all variables are randomly sampled (and of course if a one-way analysis is run, with each parameter varied in turn while others vary using seeded random numbers to account for variability).

   Multiple cohorts are run to provide an average ICER (i.e. each subgroup ICER is an average ICER across the specified number of cohorts run. For example, where 3 cohorts of 100 patients are run, each ICER generated (GL males, GL females, PL males and PL females) will be the average of the ICERs generated for each of the three cohorts. This approach aims to reduce uncertainty around model results and ensure that an individual cohort of patients generating an outlying ICER (high or low) is not taken in isolation.

   To aid interpretation, we have provided colour coding on the parameters sheet to identify which variables are randomly sampled during all analyses, and which are only randomly sampled during full probabilistic analyses.

c. The reviewer's interpretation is correct – values such as CVD_ang are only varied during full probabilistic analysis as described in part b of this answer.

B29. *Please make clear what the differences are between the Overall ICER, the adjusted overall ICER, the Cohort ICER and the Average ICER (all of which are listed in the Sim sheet of the model).*

To support the understanding of the differences between these four incremental cost-effectiveness ratios (ICERs), we have provided an example of a run of the model with 3 cohorts of 1,000 patients. Based on these number of cohorts and patients, the model will in effect run 24 cohorts – 3 cohorts for each of 4 patient sub-groups, across 2 treatment arms – each comprising 1,000 individual patients running through the model, resulting in the following permutations being run:

- Female GL patients treated with metreleptin on top of SC (3 cohorts)
- Female GL patients treated with SC alone (3 cohorts)
- Male GL patients treated with metreleptin on top of SC (3 cohorts)
- Male GL patients treated with SC alone (3 cohorts)
- Female PL patients treated with metreleptin on top of SC (3 cohorts)
- Female PL patients treated with SC alone (3 cohorts)
- Male PL patients treated with metreleptin on top of SC (3 cohorts)
- Male PL patients treated with SC alone (3 cohorts)

The 'Cohort ICER' row in the 'sim' sheet represents the results from the last cohort (third cohort in this example) to be run through the model. The 'Average ICER' row in the 'sim' sheet represents the average results from the 3 cohorts. Based on the results from these 3 cohorts, above these rows the different combinations of subgroup-level ICERs and 'Overall' row in the 'sim' sheet presents the results for the cost-effectiveness model for the subgroups and overall population (described in section 12.1.1 of the submission) representative of patients in the UK eligible for treatment with metreleptin.

The overall ICER is the output from the model for the cost-effectiveness model population, without additional weighting applied for simulations accruing >10 undiscounted incremental quality-adjusted life years (QALYs).

The final adjusted ICER (used as the base-case) is derived by applying additional QALY weighting according to the NICE Highly Specialised Technology process guide (59) to reflect significant QALY gains (>10 incremental undiscounted QALYs) in individual subgroups before creating the weighted ICER.

B30. *At various places in the electronic model numbers appear without any indication of what they refer to, and how they are used further in the calculations. Please remove any of these numbers when they are redundant, or have no use in the calculations, and indicate for the remaining numbers what they refer to.*

Redundant numbers have now been removed from the model and all remaining values have been clearly labelled.

B31. The CEAC that is provided in the model is not correct. Please update the model to produce a correct CEAC or explain the current shape of the CEAC. If the current shape is a result of number of patients and cohorts being too small, please explain what sizes are required to obtain a theoretically correct CEAC.

We have re-run the CEAC function using a higher number of patients as requested. Note that the overall CEAC is that for the combined population (GL and PL patients), which are associated with different ICERs. As such, the "stepped" shape of the overall CEAC reflects the two distinct willingness-to-pay thresholds at which one subgroup becomes cost effective, followed by the other.

B32. *In section 10.1.16 it states that as part of stopping rules as described in the SmPC for Myalepta a dose increase should be considered before stopping*

treatment. Please provide information on how many patients received such dose increases in the trial and were these accounted for in the model.

We have evaluated dose adjustments for patients in the NIH studies 991265-20010769 for patients that occurred < 1 month before treatment end. There were 4 patients identified, with 2 patients experiencing a small increase (total daily dose increased by 0.1 mL and 0.06 mL) and 2 patients reducing their dose by almost a half (total daily dose decreased by 0.5 mL for both patients). For the two patients with a dose increase, the notes state that one was due to "enrolled in new treatment protocol" and the other was due in relation to a dose re-start.

Based on the SmPC, each mL (after reconstitution) contains 5mg of metreleptin. As such the two observed dose increases in the NIH studies 991265-20001076 prior to treatment end were minimal. As such, such dose changes are unlikely to result in a larger vial being required – and therefore it is assumed that the net cost of metreleptin will not change as a result of the dose changes observed in the NIH studies 991265-200010769.

For further information in terms of how metreleptin costs have been accounted for in the model, including the titration phase, please see section 12.3.6 in the company submission and the response to clarification question B18.

B33. Priority question: *In the Model Engine sheet cells H28 and M28 are hardcoded values labelled 'Drift', and we assume that this is the per cycle increase in HbA1C. Please explain why there is no stochastic variation in this increase, given the individual patient simulation.*

Yes, the hardcodes value labelled 'Drift' is the per cycle increase in HbA1c. The HbA1c 'drift' in the model has now been added to the parameters sheet to incorporate stochastic variation under the probabilistic analysis. As a result, the cost-effectiveness analysis results have been updated and are shown at the end of the responses.

B34. Priority question: *Please provide full explanation of all hardcoded values and settings options in the Model Engine sheet, particularly for cells P24:AF55.*

Cells P24:AF55 in the model engine sheet pertain to the implementation of the stopping rule and annual discontinuation rates outlined in sections 10.1.16 and 12.2.1 of the company submission, respectively. The hardcoded values in cell U27 and cell U32 reflect the stopping rule criteria for HbA1c reduction and triglyceride reduction, respectively. Specifically, PL patients will stop treatment if the following metabolic criteria have not been met: a HbA1c reduction of at least 0.75% (absolute) from baseline, or a fasting triglyceride reduction of at least 50% from baseline. Please note that the hardcoded value in cell U34 is not used in the base-case analysis but provides an option for insulin reduction to be incorporated as part of the stopping rule criteria. The remaining hardcoded values in cells P24:AF55 have been clearly labelled and those not used in the model and have now been removed.

The hardcoded values to the right of the transition matrices for the kidney, retinopathy and retinopathy sub-models, represent β coefficients used to adjust the baseline transition probabilities for these sub-models using The Eastman's method (60), as per the formula below:

$$P_{HbA1c} = P_{HbA1c=10}(HbA1c/10)\text{^}\beta$$

The baseline probabilities $P_{HbA1c=10}$ were reported in the Sheffield diabetes paper (61) at a reference HbA1c of 10%. The equation above adjusts the risk of background retinopathy (10.10), macular oedema (1.20), proliferative retinopathy (6.30), microalbuminuria (3.25), macroalbuminuria (7.95), and neuropathy (5.30) using the β coefficients reported (shown in brackets).

These values do not vary as they are known (e.g. in the case of stopping rules) or otherwise fixed elements of an established algorithm.

B35. *In the 'Model Engine' sheet there is the option to select Caucasian while it was previously assumed that ethnicity does not have an effect on the outcome (see section 17.12.1). Please explain.*

This was incorporated in the model during the initial design stages should it have been relevant for the model. It is currently not used and has been removed due to this redundancy. As shown in 17.12.1, ethnicity is assumed to not have an effect on outcomes (assumption validated by clinical experts).

Additional evidence submission – updated cost-effectiveness results

The cost-effectiveness model has been updated in response to question B2 (baseline triglyceride), B28 (first and second order stochasticity) and B33 (HbA1c drift value being applied stochastically in the base case). As such, the updated results for the base case and scenario analyses including the patient access scheme (PAS) discount and quality-adjusted life year (QALY) weighting are summarised below.

Updated Budget Impact Analyses

The budget impact analyses were revised to account for the updated stopping rules (0% GL per year and 19.27% PL per year). At PAS price, it is estimated that the net budget impact will be [redacted] in Year 1 (2020) rising to [redacted] in Year 5 (2024) (Table 48).

Table 48: Overall lipodystrophy (GL and PL) budget impact analysis – scenario with all vial sizes available (PAS price)

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)
Medicine acquisition costs per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supportive medicines cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gross medicines costs per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Projected patient numbers likely to receive metreleptin from 2020 Addenbrooke's data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	NA	85%	90%	90%	90%
Estimated patient numbers on treatment with metreleptin (adjusted for uptake rate, non-compliance and stopping rules)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other savings / costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA, Not applicable

Please note figures have been rounded to the nearest whole £

Base case analysis

The base-case cost-effectiveness results are presented in Table 49 using the approved PAS. Metreleptin accrued [redacted] incremental QALYs and [redacted] incremental costs. This corresponds to an incremental cost-effectiveness ratio (ICER) of £179,016 per QALY gained. The ICER has been adjusted according to the NICE HST process guide (59) to reflect the significant QALY gains (>10 incremental undiscounted QALYs) for treated patients, corresponding to an ICER of £155,606. Separate results are also presented for the GL and PL cohorts. These results were based off 10 cohorts of 1000 simulated patients.

Table 49: Base-case results - discounted

Technologies	Total LY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
GL metreleptin	–	[redacted]		[redacted]	128,767 (adjusted)
PL metreleptin	–	[redacted]		[redacted]	176,253 (unadjusted)
SC overall		–	–	–	-
Metreleptin Overall		[redacted]		[redacted]	155,606 (weighted average)

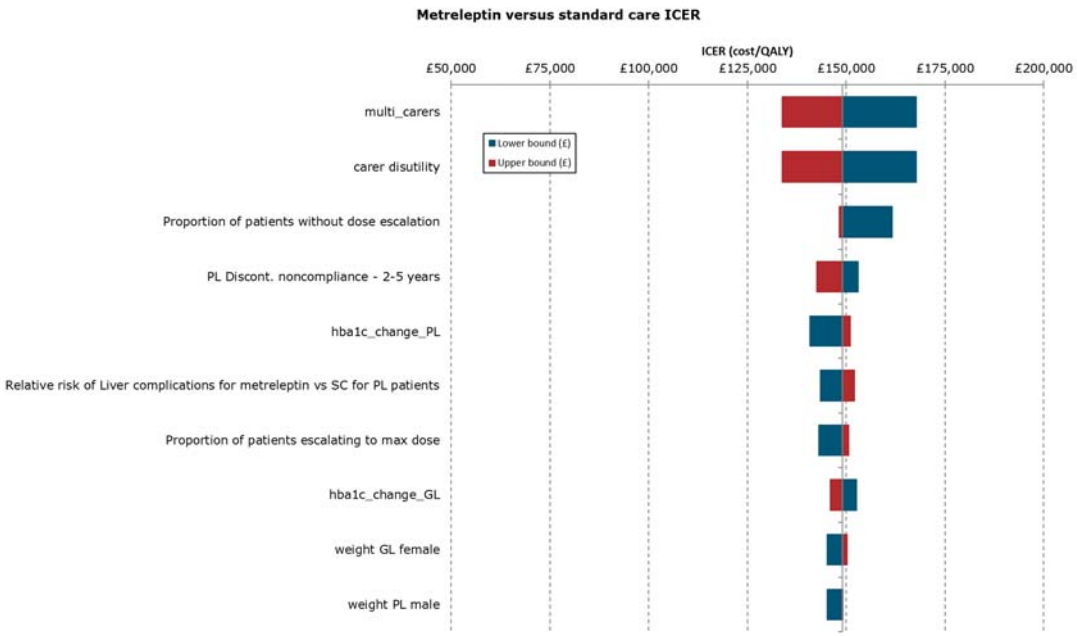
Table 50: Base-case results - undiscounted

Technologies	Total LY	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
GL metreleptin	33.96	[redacted]	7.71	[redacted]	170,598
PL metreleptin	24.73	[redacted]	1.93	[redacted]	158,372
SC overall	24.30	–	–	–	-
Metreleptin Overall	28.74	[redacted]	4.44	[redacted]	163,388 (weighted average)

Sensitivity analysis results – One-way sensitivity analysis

The results of the deterministic one-way sensitivity analysis are presented in Figure 5. One-way analyses were conducted by analysing 1 cohort of 200 patients for the base case scenario, and for each of the upper and lower bounds of each parameter. A fixed "seed" of 200 cycles worth of random values was used to ensure comparability of results – ensuring the only variation in values between each 200-patient cohort was the individual corresponding adjusted value.

Figure 5: OWSA ICER results



Sensitivity analysis results – Scenario analyses

Results of the scenario analyses for A to F outlined in section 12.4.1 company submission are presented in the table below. In addition, scenarios G and H have been included in response to B8 and B12, and scenario I has been included as referred to in the response to B26. Scenario J has been added to yield a stopping rate of approximately 35% in PL patients, which is in line the proportion of PL patients expected to stop treatment as per discussion with clinical experts at Addenbrookes (expected to be around 25% to 50%).These results were based off 5 cohorts of 1000 simulated patients. The ICERs have been adjusted according to the NICE HST process guide (59), where relevant to reflect the significant QALY gains (>10 incremental undiscounted QALYs) for treated patients.

Table 51: Scenario analysis results

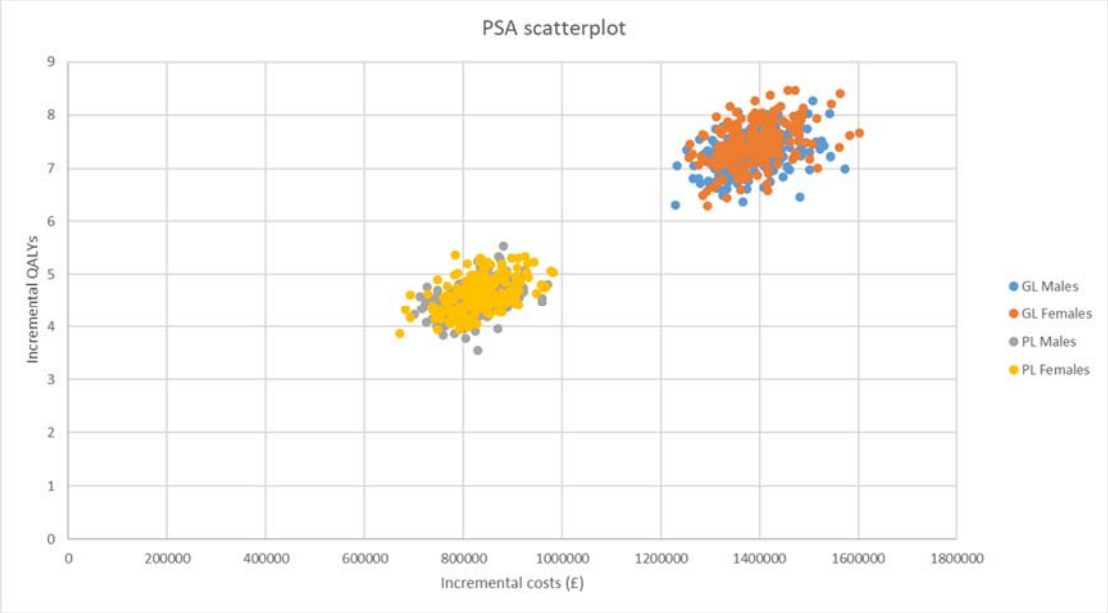
Scenario	Technologies	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
A (1.5% discount rate)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	148,822
B (ALT / AST surrogate liver outcomes)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	163,645
C (alternative HbA1c reduction: 1.52%)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	166,976
D1 (additive disutility)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	151,484
D2 (largest single utility decrement)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	164,954
E (additive mortality risk inflation)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	157,700
F (pancreatitis benefit, OR = 0.93)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	154,340
G (mean carer = 1.67) Added in response to question B12.	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	173,839
H (FED discontinuation rates: 8.93% in the first year; 5.63% in years 2 to 9; and 2.04% for year 10 and over). Alternative discontinuation rate explored in response to question B8. (43)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	141,194
I (results using combined male/female cohorts)	SC	-	-	-
	Metreleptin	[redacted]	[redacted]	156,675

J (25% additional stopping PL patients, creating 32% overall stopping rate in PL patients)	SC	-	-	-
	Metreleptin – GL patients	[redacted]	[redacted]	132,682
	Metreleptin – PL patients	[redacted]	[redacted]	156,789
	Metreleptin – all patients	[redacted]	[redacted]	146,307

Sensitivity analysis results – probabilistic analysis

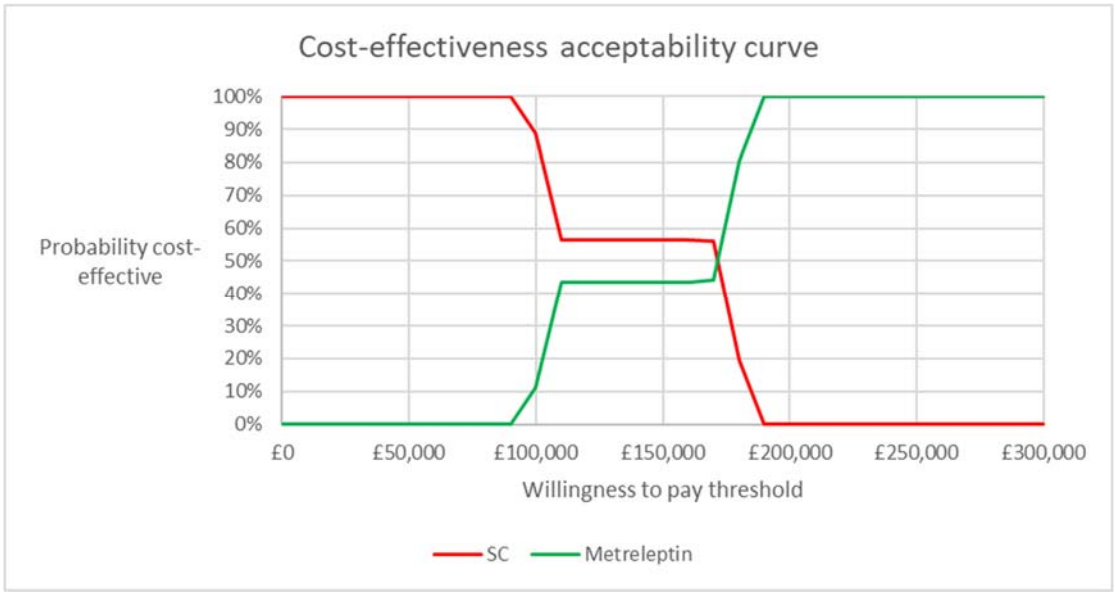
A probabilistic analysis of 200 cohorts of 250 patients per subgroup (400,000 total patients) was run. Results are shown in Figure 6.

Figure 6: Probabilistic sensitivity analysis scatterplot



A cost-effectiveness acceptability curve was run using 3 cohorts of 1,000 patients per subgroup per threshold (600,000 total patients). Results are shown in Figure 7.

Figure 7: Cost-effectiveness acceptability curve


Cost-effectiveness acceptability curve
Probability cost-effective
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
£0
£50,000
£100,000
£150,000
£200,000
£250,000
£300,000
Willingness to pay threshold
SC
Metreleptin

Validation

B36. Priority question: *Please provide more details about what validation efforts were performed and the results of these validation efforts. This could be presented for example (but not necessarily) with the help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/). Please confirm whether black-box tests to detect modelling errors were conducted. If not, please include these steps as well.*

The validation methods are described in section 12.7.1 of the company submission. As part of the validation methods used, an internal health economist independent to those who built the model conducted a quality check of the model functions and calculations. This included verifying data inputs against their sources, checking the cost year for data inputs, checking distributions assigned to parameters for sensitivity analyses, verifying and validating calculations and functionality, and conducting black-box tests.

For transparency, Model calculations and individual patient Markov traces are visible and to allow interrogation of patient progression to ensure the patient pathways and outcomes are logical, and that transitions, costs and utilities can be fully tracked on a patient by patient basis for the purpose of identifying errors. In the interest of ensuring transparency, a structured model 'walkthrough' was provided to the ERG and Technical team via videoconference on June 10, 2020.

As part of black-box testing for a patient-level simulation model of this type, extensive face validity checks using alternate settings and extreme values tests (e.g. removing elements from the model by setting to zero and confirming their absence in model results) were run to confirm expected results and identify errors.

Furthermore, analyses using identical seeded random variables were run to produce identical model results on separate runs and confirm no unexpected or unexplainable variation.

In addition, the external academic modelling expert from a leading Evidence Review Group reviewed and validated the Excel model approach and reviewed calculations for errors.

As such, the outcomes of these processes were to minimise and remove errors from the model approach.

Clinical Experts

B37. Priority question: *Please provide all relevant details of the communication between the company and the clinical experts. Please include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or teleconference, list of expert recommendations and justifications for clinical assumptions and inputs used in the model*

Following the Amryt acquisition of Aegerion in October 2019, the subsequent handover of the metreleptin NICE submission, and after a detailed analysis of the submission, we became acutely aware of the questions and issues both the ERG and the committee had and in particular, with the comparative clinical effectiveness analysis approach and cost effectiveness model. We therefore made a decision to approach the resubmission with a "no stone unturned" approach and engaging with key clinicians has been a key part of doing this.

With that in mind, we have engaged with key opinion leaders to ensure our approach to the new indirect treatment comparison and cost effectiveness model adequately addressed all of the issues raised by the ERG and committee. This has been through ad-hoc communications with clinicians at Addenbrooke's and conducting a Delphi panel including 10 international clinical experts (including 3 of which were clinical experts from Addenbrooke's Hospital) (see Section 12.3.3 of the company submission for further details on the Delphi panel).

The key roles of the clinicians involved via the ad-hoc communications from those at Addenbrooke's Hospital, the National Specialist Centre for the treatment of Lipodystrophy.

- Professor of [redacted], University of Cambridge. Director, [redacted]. Hon Consultant Physician, Addenbrookes Hospital, Cambridge.
- Professor of Molecular Metabolism, and Wellcome Trust Senior Clinical Research Fellow, University of Cambridge, Hon Consultant Physician, Addenbrookes Hospital, Cambridge.
- Consultant physician (Diabetes and endocrinology), Addenbrookes Hospital, Cambridge.

We have communicated by telephone, face to face meetings and latterly a virtual meeting. Between October 2019 and the submission date we have had three face to face and one virtual meeting with the principle meeting being in January 2020.

In addition, we have written to the clinicians asking for a statement to confirm their opinion on the indirect treatment comparison approach and results and the structure and assumptions in the model. We have asked them to forward this to Joanne Ekeledo at NICE.

Appendix 1: Additional data for lipodystrophy outcomes from smaller metreleptin studies (in response to A14)

Effect on appearance

Miehle *et al*. investigated 8 lipodystrophy patients after twelve months treatment with metreleptin. Median fat mass was significantly reduced during metreleptin treatment from 22.3 kg at baseline to 20.0 kg at 1 year ($p = 0.031$); however, body weight, body mass index, and waist-to-hip ratio were not significantly affected. Five of the six patients with familial partial lipodystrophy (FPLD) lost between 4 and 114 cm^3 of facial soft tissue volume in the pre-auricular, buccal, and submandibular area during metreleptin treatment whereas a slight volume gain was seen in one FPLD patient. The two patients with GL developed a volume loss of 20 and 8 cm^3 in the buccal region between baseline and 1 year of metreleptin therapy, respectively (62). Another publication by Vatier *et al*. supports that metreleptin replacement leads to loss of facial soft tissue volume in lipodystrophy patients (50). They assessed the patients' adherence and satisfaction with metreleptin therapy, as well as self-perception of physical appearance and social interactions, in all the 20 patients with PL and GL included in the French metreleptin compassionate program and treated for more than 1 year at the time of the study. Morphological appearance was reported improved under metreleptin therapy in 13 among 17 patients (50).

Organ damage: liver disease

In an open-label prospective study of leptin therapy in patients with inherited and acquired lipodystrophy at the NIH, liver biopsies were performed at baseline (N=50) and after leptin replacement (N=27). Of the 27 patients, 86% had borderline or definite non-alcoholic steatohepatitis (NASH) at baseline and only 33% had NASH after leptin replacement for 25.8 ± 3.7 months ($p = 0.0002$). The authors concluded that leptin appears to be a highly effective therapy for NASH in hyperleptinemic lipodystrophy patients (28).

Organ damage: Renal function

In a study by Lee *et al*. in lipodystrophy patients, the 24-hour urinary albumin and protein excretion rates, estimated glomerular filtration rate, and creatinine clearance were measured at baseline and after up to 24 months of metreleptin treatment. There were significant reductions of 83% in albuminuria and 56% in proteinuria in GL patients (63).

Hyperphagia

A study of nine lipodystrophy patients demonstrated that metreleptin treatment over 52 weeks is associated with significantly increased resting state connectivity in the both, homeostatic and hedonic brain areas accompanied by decreased hunger feelings and a diminished incentive value of food (64). Further evidence is presented by Püschel *et al*. in five female lipodystrophy patients with indication for metreleptin that long-term metreleptin treatment of >150 weeks has sustained effects on eating behaviour with increased satiety, as well as reduced hunger and hunger-related measures. On the Three Factor Eating Questionnaire, the mean value of factor 3 (hunger) significantly decreased from 9.2 ± 0.2 at baseline to 2.6 ± 1.5 at long-term assessment (7).

Appendix 2: Missingness pattern for HbA1c and triglycerides up to Month 12 in NIH studies 991265/20010769 (in response to A18)

Table 52: Evaluation Intervals for Efficacy Analysis

Evaluation	Protocol 991265 Specified Visit Interval	Protocol 20010769 Specified Visit Interval	Analysis Visit Interval
Screening/Baseline	Day 1 to Day 7	Day 1 to Day 7	Day 1 to Day 7
Day 7	Day 7 ± 3 Days	Day 7 ± 3 Days	Day 7 ± 3 Days
Day 14	---	Day 14 ± 3 Days	Day 11 to Day 14
Day 21	Day 22 ± 3 Days	Day 21 ± 3 Days	---
Month 1	Month 1 ± 1 month	Month 1 ± 1 month	Day 30 ± 15 Days
Month 2	Month 2 ± 1 month	Month 2 ± 1 month	Day 60 ± 15 Days
Month 4	Month 4 ± 2 months	Month 4 ± 2 months	Day 120 ± 30 Days
Month 6	Month 6 ± 2 months	---	Day 180 ± 30 Days
Month 8	Month 8 ± 4 months	Month 8 ± 4 months	Day 240 ± 30 Days
Month 10	Month 10 ± 4 months	---	---
Month 12	Month 12 ± 4 months	Month 12 ± 4 months	Day 365 ± 65 Days
Month 16	Month 16 ± 4 months	---	Day 485 ± 30 Days
Month 18	---	Month 18 ± 4 months	Day 545 ± 30 Days
Month 20	Month 20 ± 4 months	---	Day 605 ± 30 Days
Month 24	---	Month 24 ± 4 months	Day 730 ± 30 Days
Every 6 months post Month 24 until end of study	---	Month 24 + every 6 months	Day 760 + 180 Days per 6 months ± 60 Days

Table 53: Missingness Pattern for HbA1c, Generalised Lipodystrophy

Pattern Number	Screening/Baseline	Month 1	Month 2	Month 4	Month 6	Month 8	Month 12	Count
1	X	X	X	X	X	.	X	2
2	X	X	X	X	.	X	X	1
3	X	X	X	X	.	.	.	1
4	X	X	X	.	X	X	X	2
5	X	X	.	X	.	X	X	1
6	X	.	X	X	.	X	X	1
7	X	.	X	.	X	X	X	1
8	X	.	.	X	.	X	X	10
9	X	.	.	X	.	X	.	4
10	X	.	.	X	.	.	X	3
11	X	.	.	.	X	X	.	1
12	X	.	.	.	X	.	X	12
13	X	.	.	.	X	.	.	7
14	X	.	.	.	.	X	X	3
15	X	.	.	.	.	X	.	6
16	X	.	.	.	.	.	X	5
17	X	.	.	.	.	.	.	2

Table 54: Missingness Pattern for HbA1c, Partial Lipodystrophy

Pattern Number	Screening/Baseline	Month 1	Month 2	Month 4	Month 6	Month 8	Month 12	Count
1	X		X	X	X	.	.	1
2	X		X	.	X	X	X	1
3	X		.	X	.	X	X	7
4	X		.	X	.	.	X	3
5	X		.	X	.	.	.	1
6	X		.	.	X	.	X	9
7	X		.	.	X	.	.	5
8	X		.	.	.	X	X	3
9	X		.	.	.	X	.	2
10	X		.	.	.	.	X	9

Table 55: Missingness Pattern for Triglycerides, Generalised Lipodystrophy

Pattern Number	Screening/Baseline	Month 1	Month 2	Month 4	Month 6	Month 8	Month 12	Count
1	X	X	X	X	X	.	X	1
2	X	X	X	X	.	X	X	2
3	X	X	X	X	.	.	.	1
4	X	X	X	.	X	X	X	2
5	X	X	.	X	.	X	X	1
6	X	.	X	.	X	X	X	1
7	X	.	.	X	X	.	X	1
8	X	.	.	X	.	X	X	10
9	X	.	.	X	.	X	.	4
10	X	.	.	X	.	.	X	3
11	X	.	.	.	X	X	.	1
12	X	.	.	.	X	.	X	11
13	X	.	.	.	X	.	.	7
14	X	.	.	.	.	X	X	3
15	X	.	.	.	.	X	.	5
16	X	.	.	.	.	.	X	5
17	X	.	.	.	.	.	.	3
18	.	X	X	X	X	.	X	1

Table 56: Missingness Pattern for Triglycerides, Partial Lipodystrophy

Pattern Number	Screening/Baseline	Month 1	Month 2	Month 4	Month 6	Month 8	Month 12	Count
1	X		X	X	X	.	.	1
2	X		X	X	.	X	X	1
3	X		X	.	X	X	X	1
4	X		.	X	.	X	X	6
5	X		.	X	.	.	X	3
6	X		.	X	.	.	.	1
7	X		.	.	X	.	X	10
8	X		.	.	X	.	.	4
9	X		.	.	.	X	X	3
10	X		.	.	.	X	.	2
11	X		.	.	.	.	X	8
12	.		.	.	X	.	.	1

Appendix 3: ITC code (in response to A26)

```
#### INVERSE PROBABILITY WEIGHTING ####

#### THE FIRST TIME YOU USE THIS SCRIPT, INSTALL THESE PACKAGES ####
install.packages("readexcel")
install.packages("tableone")
install.packages("sandwich")
install.packages("survey")
install.packages("survminer")



###AFTER THAT, YOU CAN JUST LOAD THESE PACKAGES###
library(readxl)
library(tableone)
library(sandwich)
library(survey)
library(survival)
library(survminer)



setwd("")

############## HBA1C ##################
#Read data in as data frame
metreleptin_soc_hba1c <- read_excel("IPW_HbA1c.xlsx")
data.frame(metreleptin_soc_hba1c)

#change to factors
metreleptin_soc_hba1c$gender <- as.factor(metreleptin_soc_hba1c$gender)
metreleptin_soc_hba1c$ld_type <- as.factor(metreleptin_soc_hba1c$ld_type)



#probability of treatment
psmodel<- glm(treatment ~
                age + gender + ld_type, family = binomial(link = "logit"),
data = metreleptin_soc_hba1c)

ps <- predict (psmodel, type = "response")
```

```
#stabilised weights


treated = nrow(subset(metreleptin_soc_hba1c, treatment == 1))


nottreated = nrow(subset(metreleptin_soc_hba1c, treatment == 0))


ptreat<- nottreated/treated


px<- ptreat/ps


weight <- ifelse(metreleptin_soc_hba1c$treatment==1,px,(1-px))


#apply weights to data

weighteddata <- svydesign(ids = ~1, data = metreleptin_soc_hba1c, weights
= ~ weight)


metreleptin_soc_hba1c$weights=weight

metreleptin_soc_hba1c$weighteddata1 =
metreleptin_soc_hba1c$weights*metreleptin_soc_hba1c$change


#weighted table

xvars <- c("age", "gender", "ld_type")

weightedtable <- svyCreateTableOne(vars = xvars, strata = "treatment",
data = weighteddata, test = FALSE)

print(weightedtable, smd = TRUE)


#glm


glm.obj <- lm(metreleptin_soc_hba1c$change ~
metreleptin_soc_hba1c$treatment, weights = weight)


mp <- as.data.frame(cbind(hp = metreleptin_soc_hba1c$treatment,

                          predict(glm.obj, interval = 'confidence')))


#summary

betaiptw <- coef(glm.obj)


#account for weighting, using sandwich variance

SE <-sqrt(diag(vcovHC(glm.obj, type="HC0")))
```

```
#point estimate and CI for relative risk.
ate <- betaiptw[2]
lcl <- betaiptw[2] - 1.96 * SE[2]
ucl <- betaiptw[2]+ 1.96 * SE[2]
SE[2]
SE <- SE[2]
P <- summary(glm.obj)$coefficients[2,4]
results<- c(ate, SE, lcl, ucl, P)
results


############## TRIGLYCERIDES ##################
#read data in as data frame #
triglycerides <- read_excel("IPW_Triglycerides.xlsx") #Change working
directory
View(triglycerides)
 data.frame(triglycerides)
#
# #change to factors
triglycerides$gender <- as.factor(triglycerides$gender)
triglycerides$ld_type <- as.factor(triglycerides$ld_type)


# #propensity score model


psmodel<- glm(treatment ~
                  age + gender + ld_type, family = binomial(link =
"logit"), data = triglycerides)


ps <- predict (psmodel, type = "response")


# #create weights
weight <- ifelse(triglycerides$treatment==1,1/(ps),1/(1-ps))
#
# #apply weights to data
weighteddata <- svydesign(ids = ~1, data = triglycerides, weights = ~
weight)


# #weighted table
xvars <- c("age", "gender", "ld_type")
weightedtable <- svyCreateTableOne(vars = xvars, strata = "treatment",
data = weighteddata, test = FALSE)
```

```
print(weightedtable, smd = TRUE)


# #glm


glm.obj <- lm(triglycerides$change ~ triglycerides$treatment,
weights=weight)


 mp <- as.data.frame(cbind(hp = triglycerides$treatment,
                           predict(glm.obj, interval = 'confidence')))


 #summary
betaiptw <- coef(glm.obj)


# #account for weighting, using sandwich variance
SE <-sqrt(diag(vcovHC(glm.obj, type="HC0")))


# #point estimate and CI for relative risk.
ate <- betaiptw[2]
lcl <- betaiptw[2] - 1.96 * SE[2]
ucl <- betaiptw[2]+ 1.96 * SE[2]
SE[2]
c(lcl, ate, ucl)
SE <- SE[2]
P <- summary(glm.obj)$coefficients[2,4]
c(ate, SE, lcl, ucl, P)



############## ALT ##################
#read data in as data frame #
ALT <- read_excel("IPW_ALT.xlsx") #Change working directory
View(ALT)
data.frame(ALT)
#
# #change to factors
ALT$gender <- as.factor(ALT$gender)
ALT$ld_type <- as.factor(ALT$ld_type)


# #propensity score model
```

```
psmodel<- glm(treatment ~
                age + gender + ld_type, family = binomial(link = "logit"),
data = ALT)


ps <- predict (psmodel, type = "response")


# #create weights
weight <- ifelse(ALT$treatment==1,1/(ps),1/(1-ps))
#
# #apply weights to data
weighteddata <- svydesign(ids = ~1, data = ALT, weights = ~ weight)


# #weighted table
xvars <- c("age", "gender", "ld_type")
weightedtable <- svyCreateTableOne(vars = xvars, strata = "treatment",
data = weighteddata, test = FALSE)
print(weightedtable, smd = TRUE)


# #glm


glm.obj <- lm(ALT$change ~ ALT$treatment, weights=weight)


mp <- as.data.frame(cbind(hp = ALT$treatment,
                          predict(glm.obj, interval = 'confidence')))


#summary
betaiptw <- coef(glm.obj)


# #account for weighting, using sandwich variance
SE <-sqrt(diag(vcovHC(glm.obj, type="HC0")))


# #point estimate and CI for relative risk.
ate <- betaiptw[2]
lcl <- betaiptw[2] - 1.96 * SE[2]
ucl <- betaiptw[2]+ 1.96 * SE[2]
SE <- SE[2]
P <- summary(glm.obj)$coefficients[2,4]
c(ate, SE, lcl, ucl, P)
```

```
############## AST ##################
#read data in as data frame #
AST <- read_excel("IPW_AST.xlsx") #Change working directory
View(AST)
data.frame(AST)
#
# #change to factors
AST$gender <- as.factor(AST$gender)
AST$ld_type <- as.factor(AST$ld_type)

# #propensity score model

psmodel<- glm(treatment ~
                age + gender + ld_type, family = binomial(link = "logit"),
data = AST)

ps <- predict (psmodel, type = "response")

# #create weights
weight <- ifelse(AST$treatment==1,1/(ps),1/(1-ps))
#
# #apply weights to data
weighteddata <- svydesign(ids = ~1, data = AST, weights = ~ weight)

# #weighted table
xvars <- c("age", "gender", "ld_type")
weightedtable <- svyCreateTableOne(vars = xvars, strata = "treatment",
data = weighteddata, test = FALSE)
print(weightedtable, smd = TRUE)

# #glm

glm.obj <- lm(AST$change ~ AST$treatment, weights=weight)

mp <- as.data.frame(cbind(hp = AST$treatment,
                          predict(glm.obj, interval = 'confidence')))

#summary
betaiptw <- coef(glm.obj)
```

```
# #account for weighting, using sandwich variance
SE <-sqrt(diag(vcovHC(glm.obj, type="HC0")))


# #point estimate and CI for relative risk.
ate <- betaiptw[2]
lcl <- betaiptw[2] - 1.96 * SE[2]
ucl <- betaiptw[2]+ 1.96 * SE[2]
SE <- SE[2]
P <- summary(glm.obj)$coefficients[2,4]
c(ate, SE, lcl, ucl, P)


############## PANCREATITIS ##################
#read data in as data frame #
pancreatitis <- read_excel("IPW_Pancreatitis.xlsx") #outcome working
directory
View(pancreatitis)
data.frame(pancreatitis)
#
# #outcome to factors
pancreatitis$gender <- as.factor(pancreatitis$gender)
pancreatitis$ld_type <- as.factor(pancreatitis$ld_type)


# #propensity score model


psmodel<- glm(treatment ~
                 age + gender + ld_type, family = binomial(link = "logit"),
data = pancreatitis)


ps <- predict (psmodel, type = "response")


# #create weights
weight <- ifelse(pancreatitis$treatment==1,1/(ps),1/(1-ps))
#
# #apply weights to data
weighteddata <- svydesign(ids = ~1, data = pancreatitis, weights = ~
weight)


# #weighted table
xvars <- c("age", "gender", "ld_type")
```

```
weightedtable <- svyCreateTableOne(vars = xvars, strata = "treatment",
data = weighteddata, test = FALSE)
print(weightedtable, smd = TRUE)


# #glm


glm.obj <- lm(pancreatitis$outcome ~ pancreatitis$treatment,
weights=weight)


mp <- as.data.frame(cbind(hp = pancreatitis$treatment,
                          predict(glm.obj, interval = 'confidence')))


#summary
betaiptw <- coef(glm.obj)


# #account for weighting, using sandwich variance
SE <-sqrt(diag(vcovHC(glm.obj, type="HC0")))


# #point estimate and CI for relative risk.
ate <- betaiptw[2]
OR <- exp(betaiptw[2])
lcl <- betaiptw[2] - 1.96 * SE[2]
ucl <- betaiptw[2]+ 1.96 * SE[2]
SE <- SE[2]
P <- summary(glm.obj)$coefficients[2,4]
c(ate, OR, SE, lcl, ucl, P)




############### PANCREATITIS IMPUTED ##################
#read data in as data frame #
pancreatitis <- read_excel("IPW_Pancreatitis_Imputed.xlsx") #outcome
working directory
View(pancreatitis)
data.frame(pancreatitis)
#
# #outcome to factors
pancreatitis$gender <- as.factor(pancreatitis$gender)
pancreatitis$ld_type <- as.factor(pancreatitis$ld_type)
```

```
# #propensity score model


psmodel<- glm(treatment ~
                 age + gender + ld_type, family = binomial(link = "logit"),
data = pancreatitis)


ps <- predict (psmodel, type = "response")


# #create weights
weight <- ifelse(pancreatitis$treatment==1,1/(ps),1/(1-ps))
#
# #apply weights to data
weighteddata <- svydesign(ids = ~1, data = pancreatitis, weights = ~
weight)


# #weighted table
xvars <- c("age", "gender", "ld_type")
weightedtable <- svyCreateTableOne(vars = xvars, strata = "treatment",
data = weighteddata, test = FALSE)
print(weightedtable, smd = TRUE)


# #glm


glm.obj <- lm(pancreatitis$outcome ~ pancreatitis$treatment,
weights=weight)


mp <- as.data.frame(cbind(hp = pancreatitis$treatment,
                          predict(glm.obj, interval = 'confidence')))


#summary
betaiptw <- coef(glm.obj)


# #account for weighting, using sandwich variance
SE <-sqrt(diag(vcovHC(glm.obj, type="HC0")))


# #point estimate and CI for relative risk.
ate <- betaiptw[2]
OR <- exp(betaiptw[2])
lcl <- betaiptw[2] - 1.96 * SE[2]
```

```
ucl <- betaiptw[2]+ 1.96 * SE[2]

SE <- SE[2]

P <- summary(glm.obj)$coefficients[2,4]

c(ate, OR, SE, lcl, ucl, P)



### MORTALITY ###

metreleptin_soc_mortality <- read_excel("IPW_Mortality.xlsx") #Change
working directory

data.frame(metreleptin_soc_mortality)


#change exposures to factor

gender <- as.factor(metreleptin_soc_mortality$gender)

GLPL_type <- as.factor(metreleptin_soc_mortality$ld_type)

study_type <- as.factor(metreleptin_soc_mortality$treatment)

age <- as.numeric(metreleptin_soc_mortality$age)

mortality <- as.factor(metreleptin_soc_mortality$CENSOR)

survtime <- as.numeric(metreleptin_soc_mortality$TIME)


id <- metreleptin_soc_mortality$ID


#propensity score model

psmodel <- glm(study_type ~ age + gender + GLPL_type, family =
binomial(link = "logit"))


ps <- predict (psmodel, type = "response")


#create weights

weight <- ifelse(study_type==1,1/(ps),1/(1-ps))


#apply weights to data

weighteddata <- svydesign(ids = ~1, data = metreleptin_soc_mortality,
weights = ~ weight)


#weighted table - IGNORE SAMPLE SIZES AS THEY ARE WEIGHTED

xvars <- c("age", "gender", "ld_type")

weightedtable <- svyCreateTableOne(vars = xvars, strata = "treatment",
data = weighteddata, test = FALSE)

print(weightedtable, smd = TRUE)
```

```
#weighted cox regression model


mortalitymodel_ipw <- coxph(Surv(survtime, mortality) ~
as.factor(treatment), id=id,
                            weights = weight, data =
metreleptin_soc_mortality)
mortalitymodel_ipw


fit <- survfit (Surv(TIME, CENSOR)~ as.factor(treatment), id=id,
                weights = weight, data = metreleptin_soc_mortality)
fit



#plot km curves
ggsurvplot(fit, data = metreleptin_soc_mortality, risk.table = TRUE,
           conf.int = TRUE,
           ylab = "Proportion surviving", xlab = "Time (years)",
           legend.title = "Treatment",
           legend.labs = c("SC", "Metreleptin"),
           palette = c("#df4114","#658B34"))
```

Appendix 4: Positivity assumption (in response to A28)

Figure 8: Propensity score distribution in HbA1c outcome

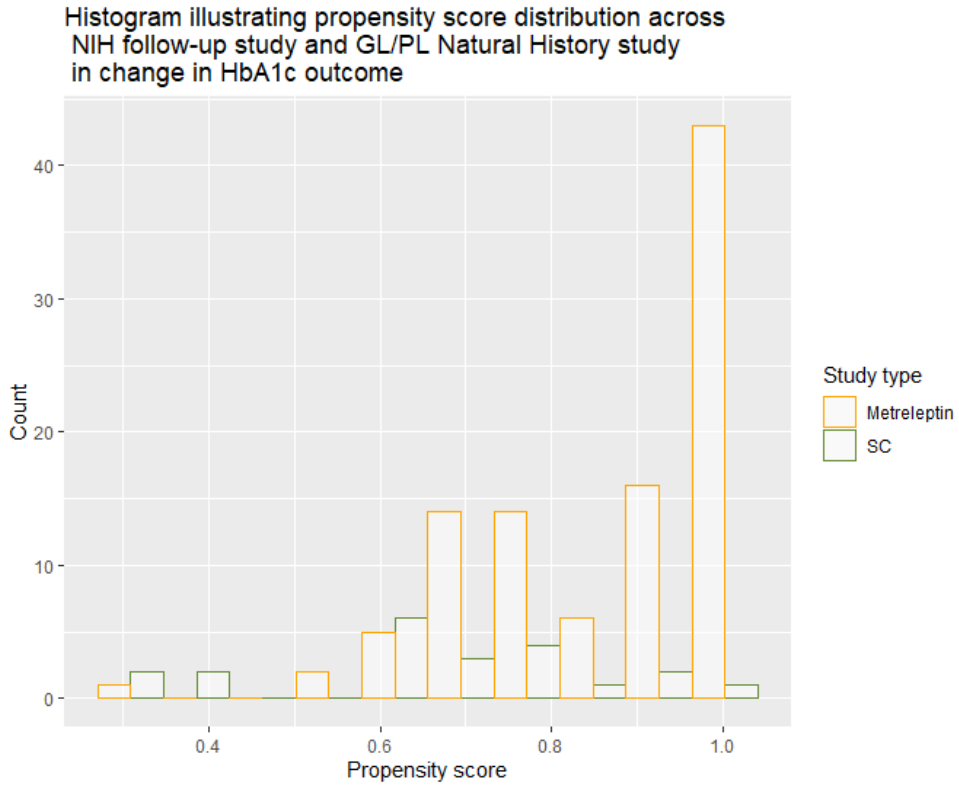


Figure 9: Propensity score distribution in triglyceride outcome

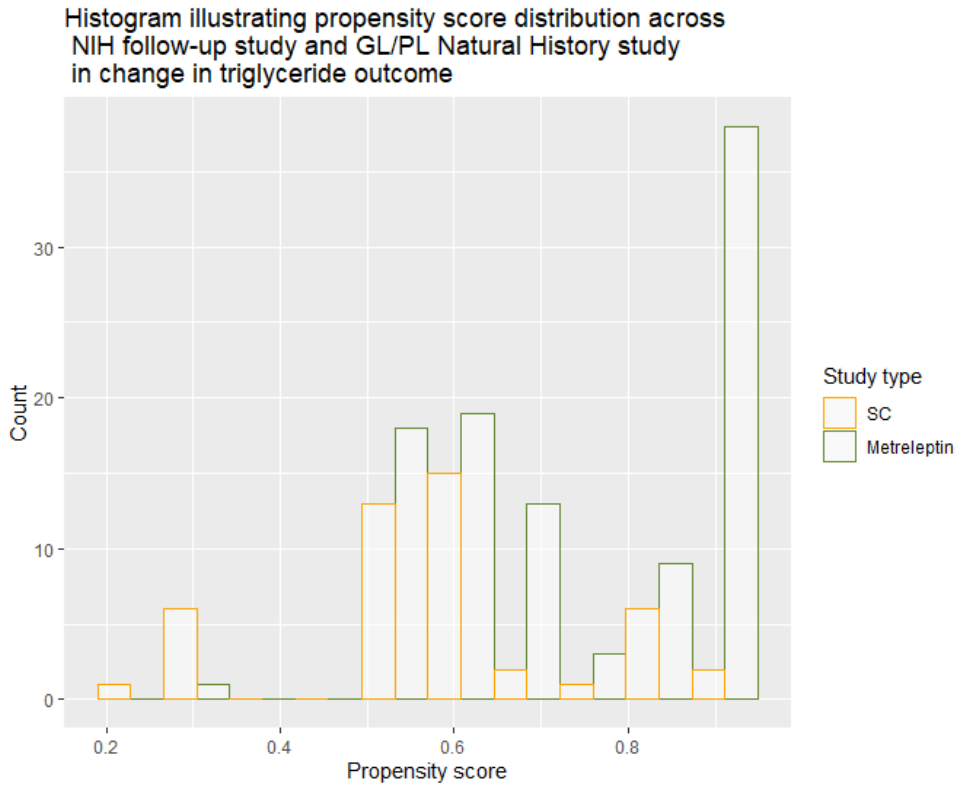


Figure 10: Propensity score distribution in ALT outcome

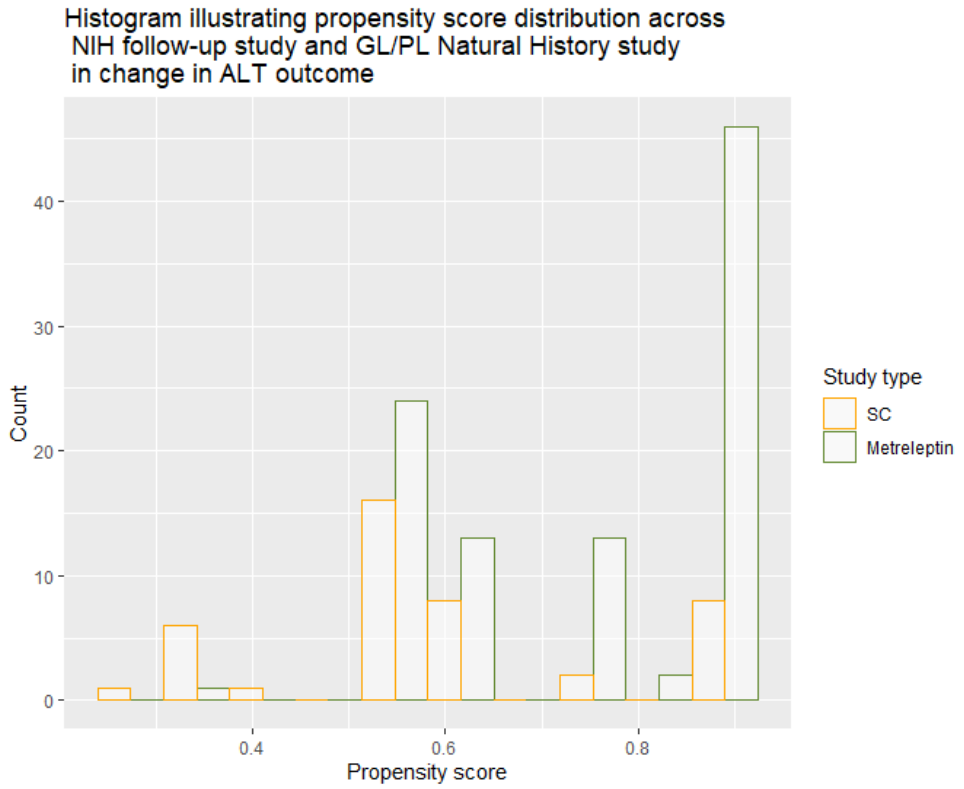


Figure 11: Propensity score distribution in AST outcome

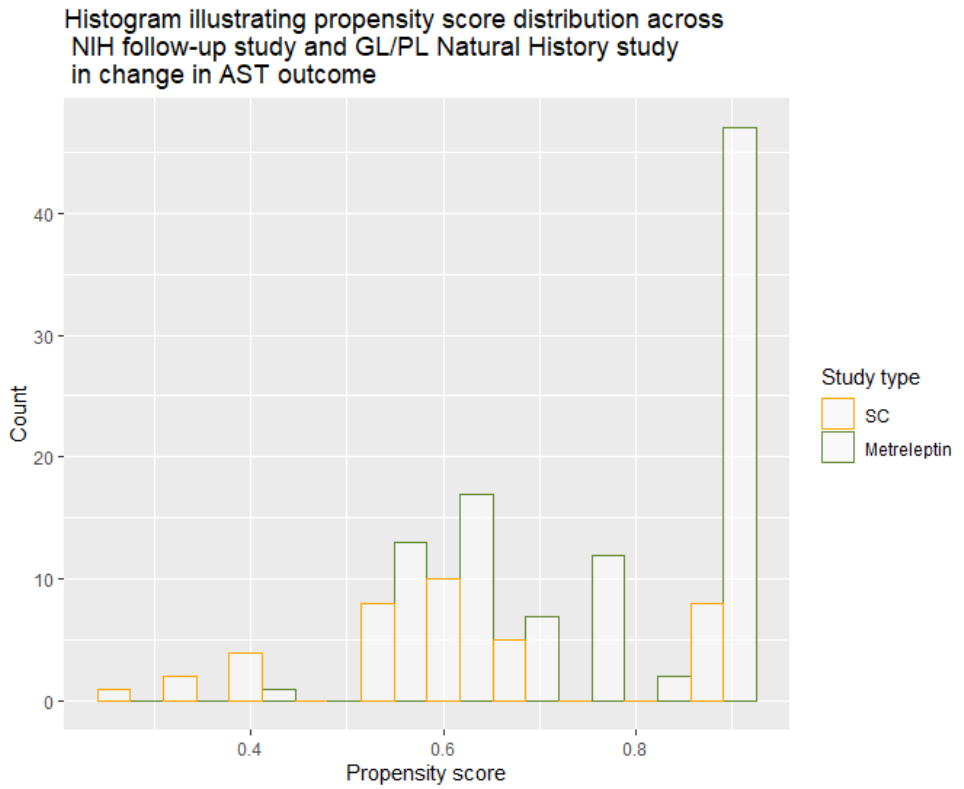
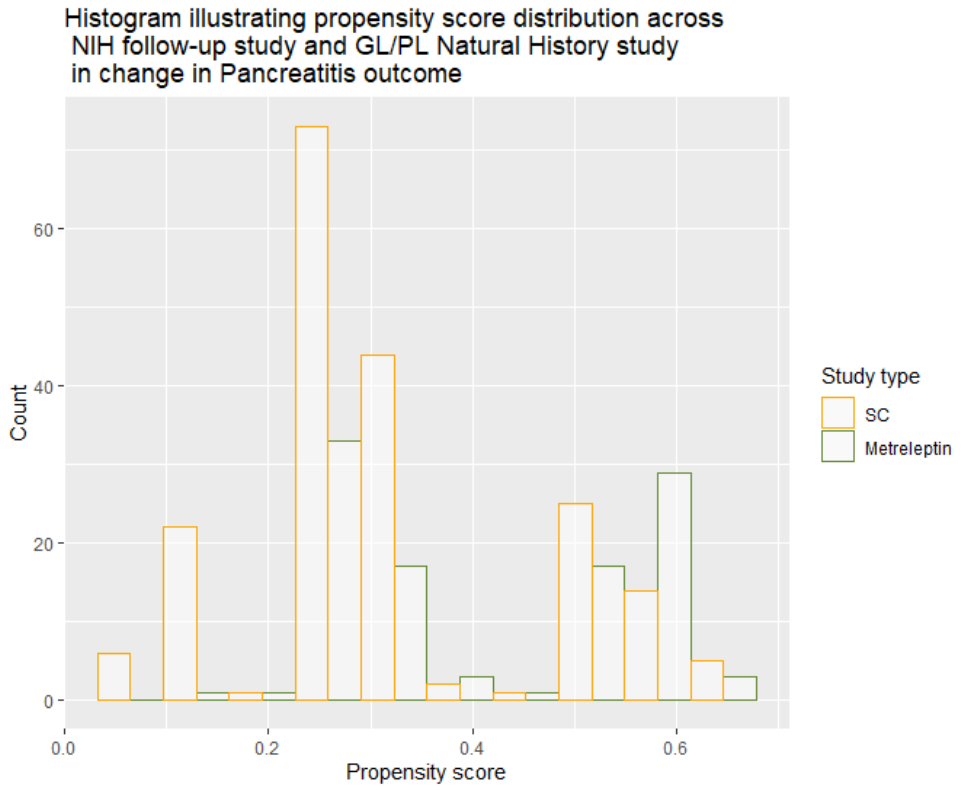


Figure 12: Propensity score distribution in pancreatitis outcome



F

Figure 13: Propensity score distribution in imputed pancreatitis outcome

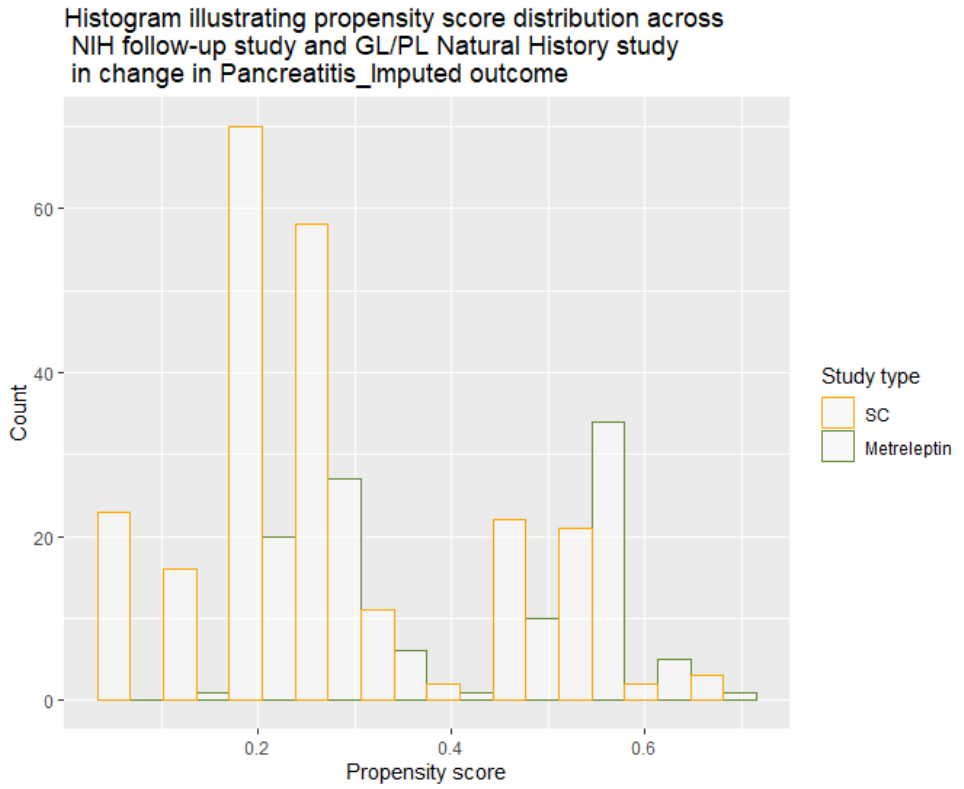
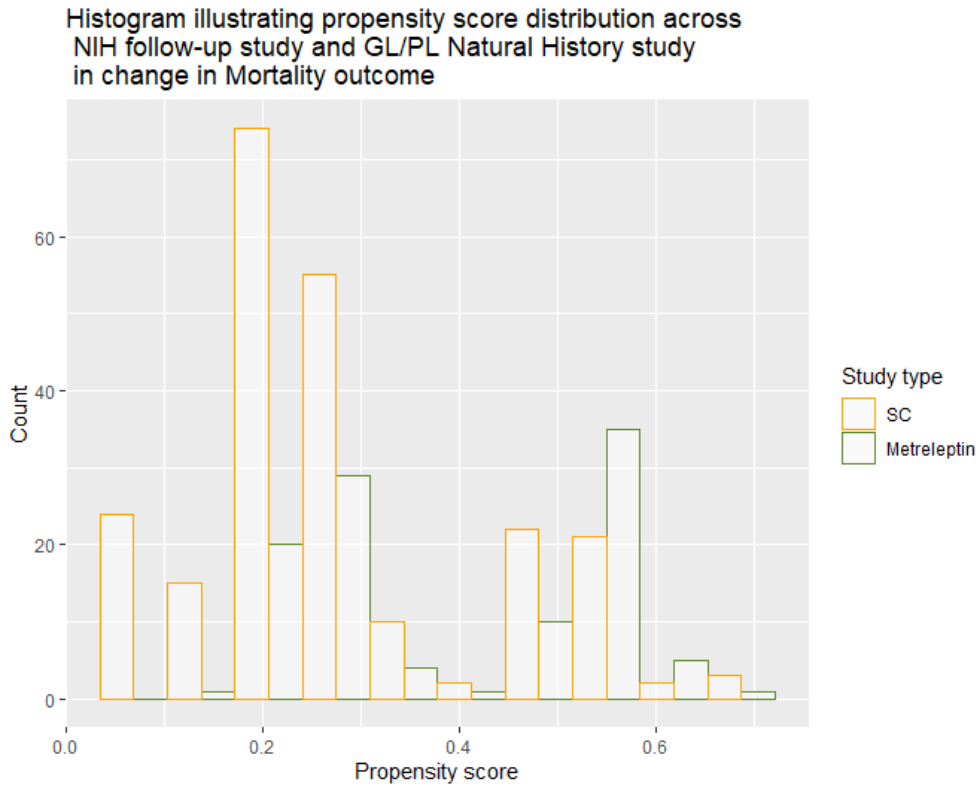


Figure 14: Propensity score distribution in mortality outcome



Appendix 5: Transformed outcome distributions (in response to A40)

Figure 15: Transformed distribution of change in HbA1c, Shapiro-Wilk W=0.97, p=0.009

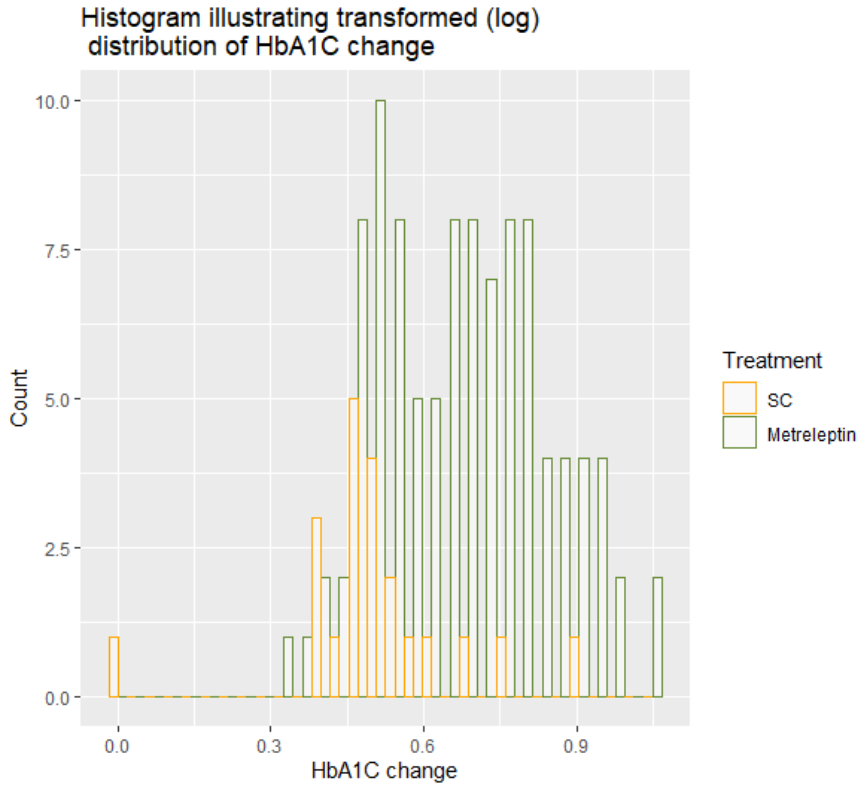


Figure 16: Transformed distribution of change in triglycerides, Shapiro-Wilk W=0.602, p < 0.001

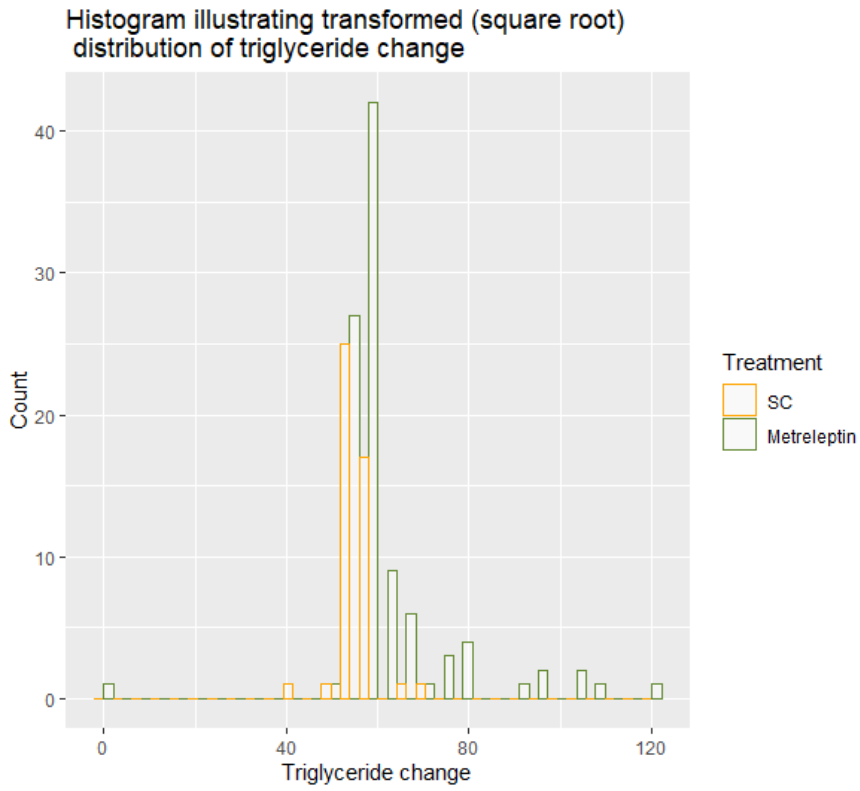


Figure 17: Transformed distribution of change in AST, Shapiro-Wilk W=0.78, p<0.001

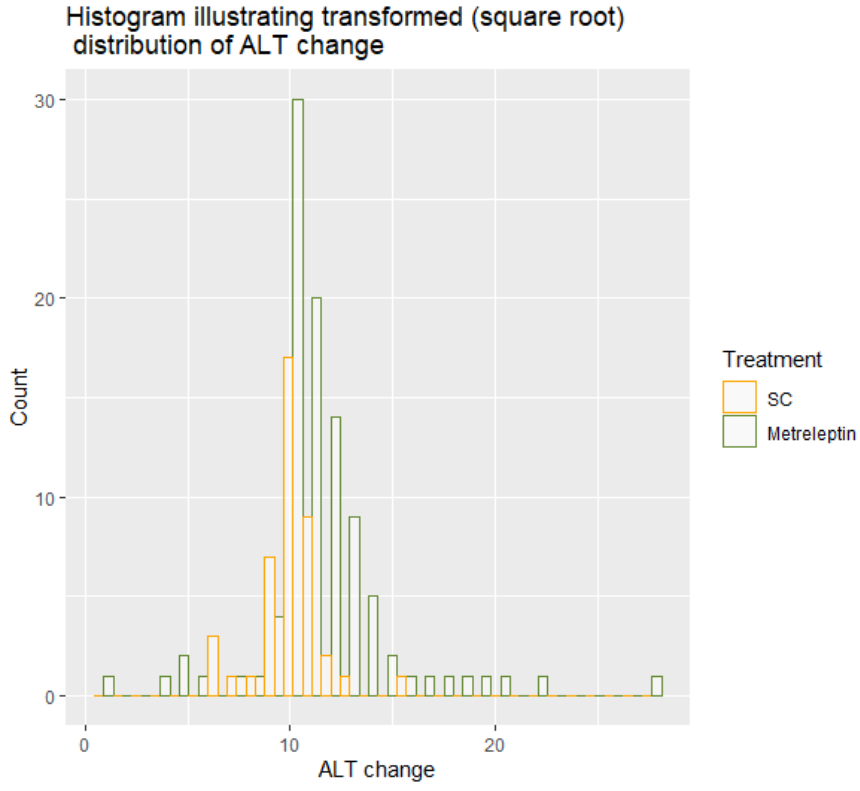
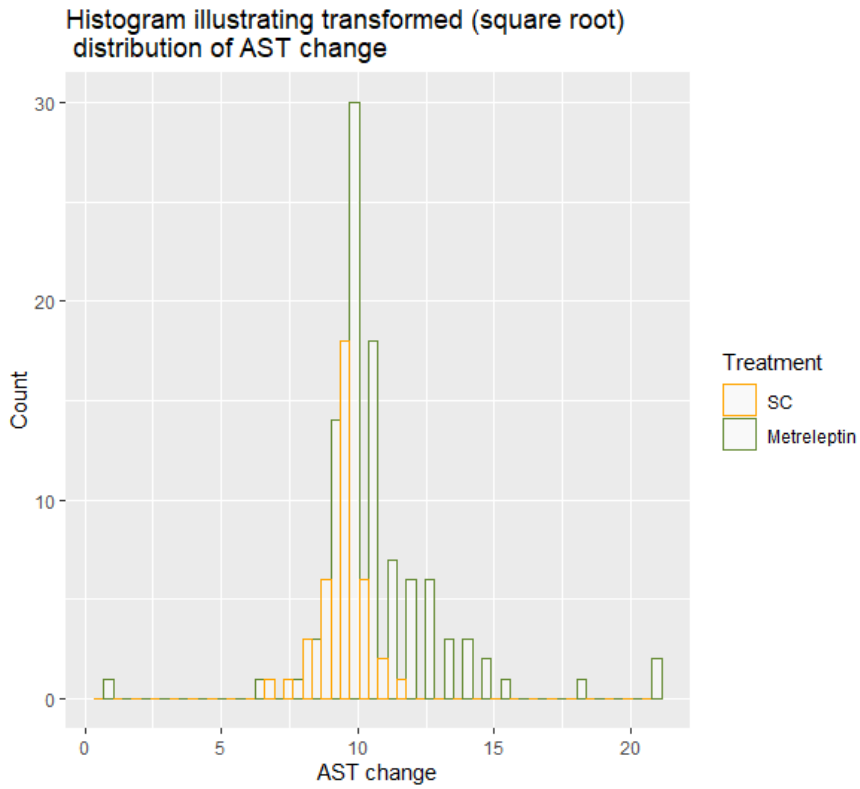


Figure 18: Transformed distribution of change in AST, Shapiro-Wilk W=0.81, p<0.001



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NICE National Institute for Health and Care Excellence

Patient organisation submission

Metreleptin for treating lipodystrophy [ID861]

Thank you for agreeing to give us your organisation's 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 submission

- 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	Diabetes UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Diabetes UK is a patient organisation representing people living with, affected by and at risk of all types of diabetes and their carers. Details of our funding can be found here: http://apps.charitycommission.gov.uk/Accounts/Ends99/0000215199_AC_20181231_E_C.PDF.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Diabetes UK has not received funding from the manufacturer of this technology or manufacturers of comparator products in the past 12 months

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Diabetes UK has no links, direct or indirect, with the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Diabetes UK spoke to healthcare professionals working with patients with lipodystrophy and conducted desk-based research to make this submission. Diabetes UK regularly speaks to people living with and affected by diabetes about their views and experiences surrounding the condition, including their concerns about treatments, diabetes-associated complications and the psychological impact the condition can have.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lipodystrophy can be a distressing and difficult condition to live with and affects both adults and children. The psychological impact of some of its physical manifestations, the intensive diet required and complex medication regime are some of the considerable burden patients with the condition can face. Most people with Lipodystrophy will have severe insulin resistance and develop diabetes mellitus. Treatment for diabetes in patients with Lipodystrophy involves a range of diabetes medication and it often progresses to the use of insulin intensive therapy, meaning four or more injections a day. This often requires large doses of insulin because of the patient's lipodystrophy-associated insulin resistance. Suboptimal management of diabetes, including for patients with lipodystrophy, has a number of associated complications. These include retinopathy, nephropathy and diabetic foot ulcers. We know that patients can find the knowledge of these potential complications very difficult and problems managing

	blood glucose levels can increase this diabetes-related distress they experience – this will also be the case for people with lipodystrophy-related diabetes.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	
8. Is there an unmet need for patients with this condition?	We understand that Metreleptin is currently the only available treatment to directly treat Lipodystrophy. Current treatment involves treating the manifestations of the disease, including cosmetic surgery, diabetes medication, and hypolipidaemic therapies. While we know that some patients in the UK are using it, the NICE decision not to recommend the treatment in 2018 has meant no new initiations onto Metreleptin have since taken place at the main Lipodystrophy service in England. This means that a significant number of patients are not being given access to a treatment that has the potential to significantly improve quality of life and clinical outcomes. We consider this a clear unmet need for many patients with lipodystrophy.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We have been told by clinicians working with patients with lipodystrophy that Metreleptin can reduce the need for insulin intensive therapy in patients with lipodystrophy and diabetes mellitus, potentially offering the opportunity for de-escalation of the treatment. Improvements in HbA1c and time-in-range have been seen in a clinic setting with the use of Metreleptin too. This treatment replaces the leptin in lipodystrophy patients who are deficient of the hormone, offering significant improvements in quality of life by reducing the symptoms associated with leptin deficiency. In addition, Metreleptin also has benefits in reducing triglycerides and liver fat in patients with lipodystrophy. Metreleptin is the only condition-specific treatment for lipodystrophy and reduces the need for other secondary treatments, like insulin intensive therapy. We know that some of these secondary treatments can place a significant burden on all areas of a persons' life. This treatment can offer patients with lipodystrophy significant hope, better clinical outcomes and an improved quality of life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We understand that there may be an increased risk of hypoglycaemia with the use of Metreleptin. However, we would expect considerable clinical input for those using Metreleptin and for support to be offered for them to manage their blood glucose levels while using the treatment.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This solution is applicable, more or less equally, to the patient groups identified with this condition (despite their disparate aetiologies). While clinical trial evidence and real-world experience generally suggests that clinical benefit for Metreleptin is more pronounced in patients with generalised lipodystrophy, some patients with partial lipodystrophy have also seen a significant positive clinical response when using this treatment. 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 specialist centres.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As Metreleptin offers the only known direct treatment for Lipodystrophy, a decision not to recommend it would have a negative impact on people who could be defined as having a disability (protected characteristic) resulting from a long-term condition.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Many patients with lipodystrophy will be aware of Metreleptin as a treatment option. It is important to note the psychological impact that knowing this treatment exists but is not available on the NHS will have on patients and their families. While we appreciate that not all people with lipodystrophy would want to use Metreleptin injections, we suggest that making this treatment available would offer patients a choice in their care – something that should be promoted by our health services and NICE.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Metreleptin can improve HbA1c and Time in Range for patients with lipodystrophy and diabetes mellitus
- Metreleptin offers a treatment option that can significantly improve quality of life for patients
- Patients with diabetes mellitus often do not want to use insulin intensive therapy, where this can be avoided
- There may be a significant negative psychological impact on patients who know Metreleptin is a treatment option, but for whom it is not available
- Metreleptin offers patients choice in their treatment

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Metreleptin for treating lipodystrophy [ID861]

Thank you for agreeing to give us your organisation's 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 submission

- 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	Lipodystrophy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lipodystrophy UK is the only charity in the UK dedicated to supporting people affected by Lipodystrophy. Our mission is to raise awareness, support those who may be affected by Lipodystrophy and advocate for excellent treatment and care. We also aim to promote and facilitate any type of research that is most likely to improve the lives of those affected. The charity is funded mainly by community donations, and from a one-off consultation with pharma (33% of total monies raised). There are currently four trustees and while not a membership organisation, we have over 100 UK followers.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	We are in regular touch with patients and carers and systematically collect information and data, informally and formally, on disease burden and treatment perspectives. Given that we are in regular contact with the majority of patients and carers affected, we believe we have a very good understanding of the impact of Lipodystrophy. To support this submission, we conducted an online survey of our community to collect information about their experiences, the impact of the disease on their lives and their goals and concerns about treatment. We had 30 respondents, 27 (90%) or which were patients, two (7%) were caregivers and 1 (3%) was both a patient and a caregiver. 25 (83%) respondents had familial partial lipodystrophy (FPLD), with one (3%) patient each with congenital generalised lipodystrophy (CGL), acquired generalised lipodystrophy (AGL), acquired partial lipodystrophy (APL) and atypical progeroid lipodystrophy. One patient was unsure of their diagnosis. A copy of the full survey responses is attached.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lipodystrophy is a group of conditions characterised by a loss of functional subcutaneous adipose tissue. As a result, the capacity for adipose tissue to store excess calories is reduced as the fat cells themselves are abnormal or absent, leading to the accumulation of ectopic fat. This ectopic fat may cause a number of multi-system complications, which have significant and debilitating impacts on the lives of patients and their carers. The amount of fat loss generally determines the severity of complications. Key symptoms include early and highly treatment resistant diabetes, severe hypertriglyceridemia, hepatic steatosis, hepatosplenomegaly, extreme hyperphagia, acanthosis nigricans, and in women, polycystic ovarian syndrome. Living with a chronic, progressive and incurable disease puts a huge strain on the emotional and psychological well-being of patients and caregivers, and the impact of altered physical appearance and subsequent body confidence due to the changes in subcutaneous adipose tissue further exacerbate the mental health of those affected. Of the survey respondents, 17 (57%) waited more than 10 yrs for their lipodystrophy diagnosis, with 21 (70%) waiting more than 5 yrs. On average, patients received between 2-3 misdiagnoses before the correct diagnosis. **Lipodystrophy has a very high burden on patients: multiple comorbidities affect all aspects of life** The average number of metabolic complications experienced was between 7 and 8. The three most prevalent were hepatic steatosis (28, 93%), high cholesterol (27, 90%) and diabetes (25, 83%). However, a large array of complications was reported, including cardiovascular disease, high blood pressure, pancreatitis, neuropathy, eruptive xanthomas, PCOS and other organ damage. 11 (37%) patients reported experiencing at least one episode of pancreatitis. Of those, the average number of episodes suffered was 6-7, with one patient reporting 25+ episodes of pancreatitis, and three reporting 9+ episodes. On average, patients have been hospitalised 2-3 times with

	pancreatitis. On average, patients described between 6 and 7 additional symptoms, with 26 (87%) experiencing fatigue/brain fog, 25 (83%) reporting musculoskeletal issues and 24 (80%) suffering with low body confidence. Between 50 and 80% of respondents reported pain (77%), mental health difficulties (77%), hyperphagia (73%) and restless legs (53%). 14 patients (47%) also reported sleep apnea. **Patients experiencing pain express common themes, suffering tremendously on a daily basis** "My body hurts ALL the time… I can't walk or stand for long, because I have no fat on my feet. My back and hips hurt all the time. I have constant, contentious bloating and abdominal pain." "I experience a high level of discomfort every day. The smallest tasks cause body pains that are equivalent to the pain you get after a weight training session. For example, if I carry bags of shopping, the next day my arm muscles would be painful and would shake even if I tried to lift something light" "I get muscle & joint pains daily due to less fat on my body, my feet get very sore as there is less padding underneath thus is painful when standing and walking" "I suffer everyday with pain, I take pre-gablin to try and manage my pain. I struggle with work so much as the pains I get are ridiculous sometimes. I have a good day then the next two are bad for me." "I get moderate abdominal pain resulting in severe discomfort and inability to eat for long hours till the pain subsides. This is a major challenge as Lipodystrophy causes frequent and severe hunger which is difficult to control especially if suffering abdominal pain. In addition to this, I get pain in my muscles, joints and limbs meaning that I am unable to carry out even the simpler tasks on a daily basis depending on severity of pain. Furthermore, my feet and legs get extremely sore due to walking even short distances as there is very little fat (padding) which is required to protect our feet from hard surfaces." 90% (27) of respondents reported making significant changes to their diet in order to try and manage their lipodystrophy. Approaches generally include low fat, carb and calorie combinations, with some patients restricted to 20-30 g of fat per day. (PHE recommends[1] <97g (males) or 78g (females) fat/day for 11-64 yr olds) In the last 12 months, 25 (83%) respondents described having one or more outpatient appointments and/or GP appointments related to lipodystrophy, with 3 (10%) having between 10 and 15 appointments, and 4 (13%) having more than 15 appointments in the last 12 months.

[1] Government recommendations for energy and nutrients for males and females aged 1 – 18 years and 19+ years. [Published 2016]

	Lipodystrophy has a massive impact on patients' ability to perform at work or school "I struggle a lot with work, but I feel no one understands when I say I'm struggling or in pain as I'm only 27 and should be 'fit and healthy'" "It is greatly affecting me. I work in a fast-paced role. The brain fog and fatigue are hindering me so badly, and getting progressively worse, that I fear the day will come when I lose my job." "Fatigue and pain forced me to give up work in 2012. Attempted to return to work in 2015 unsuccessfully due to LD symptoms and depression." "I work full time but then spend weekends sleeping to recover. Had high level of sickness [leave]" "Not working retired through ill health exhaustion, pain and digestive issues" "I gave up work in 2009 as the fatigue simply beat me - my quality of life was poor " "It impacts it so much. Both my endo and therapist suggested that I stop working to concentrate on my health." "Significant impact prior to metreleptin. I could not work full time due to poor health and energy. With treatment I am able to work full time." "I am retired due to ill health/not fit for work. I was retired on ill health grounds age 53" "Cannot work due to extreme pain and tiredness" "I am a full-time teacher, considering leaving the profession due to chronic health issues related to lipodystrophy. I don't feel that I can perform my best as a teacher. On high pain days I cannot move around the room to support students, and chronic fatigue makes prepping difficult and occasionally makes me irritable" "I get so tired that it is hard to keep awake when I'm working. The brain fog can affect my capability to perform at my full potential and can leave me prone to missing things and making mistakes." "I cannot work more than 5 hours straight due to extreme fatigue, Hypos, ability to focus" "I had a difficult time learning through school as I was so hungry." All 30 respondents reported a psychological impact of lipodystrophy on their daily lives. The top four issues reported were body confidence (25, 83%) and equally reported (23, 77%) anxiety, depression and stress. On average, between 5 and 6 psychological symptoms were reported per patient. 27 (90%) respondents reported impact of lipodystrophy on their daily life due to lack of energy, motivation and/or fatigue.

	There is a high psychological impact on the daily lives of patients and their families "Some days I feel like this disease sucks the life out of me and I can feel so low and worthless. At very bad times I can feel like I'd be better off not here. When these feelings happen, I have to bottle this all up inside and try to carry on with my daily routine. It can take just about everything out of me going to work and putting on a charade that when I get home I can't eat or socialise. I just have to go to bed." "You just never know what will happen and when, so you are always on your guard mentally and physically" "Struggle to feel like a good mom and wife because I have no energy, little libido, and always hurting" "I am constantly concerned about how others view me physically and the judgements that are made. I feel unable to date due to my body confidence" "I worry every day about the "what ifs" for myself and my family. This often makes my mood low" "It has totally taken over my life as I constantly worry about what complication of lipodystrophy I am going to suffer from next" "As Lipodystrophy is a very life limiting condition, it is a constant battle to stay strong, it has affected every single aspect of my life to socialising, career, education, forming relationships, self-care, carrying out day-to-day tasks, household chores. It is therefore not easy to stay sane at times when all your life opportunities are taken away or are limited." "I get so tired that often by the time I get home from work I am good for nothing; I have no energy even to cook properly & so my diet can be impacted badly. Instead of making use of my evenings & weekends for practical chores, or even enjoyable activities or socialising, I often find I have no energy & have to rest. This is very frustrating, adds to the feeling of being lonely & overwhelmed & means I fall behind on important things" "I struggle with my mental health. This diagnosis has been a little like grieving - for the person I should/could have been. I find it difficult to open up to people and because of my body image issues, I have never been in an intimate relationship, despite approaching 40 years old. It can be hard to stay positive when it feels like all the life has been sucked out of you. I am constantly in pain and anxious about what the future holds." **Lipodystrophy impact all aspects of patients' lives, including personal relationships** "I rarely do anything apart from work and rest." "impact on my first marriage was devastating. My ex-husband accused me of using it as an excuse to "be lazy"." "The randomness of some days of fatigue or high pain levels means plans have been frequently cancelled and

	friendships have been damaged by this." "Often cannot participate in activities or go out due to lack of energy so not having a fulfilled life - this can create tension with partner and other family members and friends" "Hard to be a wife and mother when I can barely care for myself; financially impacts too" "You don't have a relationship, who wants a freak who has no future, will die early" "I find it difficult to open up to people and because of my body image issues. Family struggle to understand how I feel (physically and emotionally) which can sometimes put a strain on those relationships. I find it very difficult to make friends and my social circle is practically non-existent" "I cannot play with my daughter (7yo) as much and as often as I want. I feel like she misses out on a lot. My husband gets frustrated at times as the lion's share of housework falls to him. Both he and my daughter worry a lot when I become unwell and this is very distressing for them." "They find it hard to notice when I'm struggling because I don't look ill." "Restricted my partners activities as he constantly worries about how I am and is unwilling to be away from me" "They need to help me a lot, so they don't have a lot of free time to do the things they want to do"
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is significant unmet need in current treatment. Available treatments are generally supportive in nature; aimed at managing symptoms only. These treatments have sub-optimal efficacy and none are disease modifying. The available treatment has been the mainstay care pathway since therapy for lipodystrophy began, with no interruption of the status quo, which compounds the frustration, lack of hope and mental wellbeing impact felt by patients and caregivers. On average, survey respondent's reported taking 5-6 medications to manage their symptoms. One patient reported taking 14 different medications. Patients frequently voice the inefficacy of most treatments and struggle to maintain good diabetic control, despite the number of medications taken. In addition, several of these medications result in unpleasant side-affects, contributing to disease burden. For example, due to severe insulin resistance, patients often inject very high doses of insulin. This can be very painful to inject as the volumes are large, the high levels in the body exacerbate acanthosis nigricans, such high doses are potentially dangerous and anecdotally, increase fatigue and hyperphagia. Patients struggle to maintain the highly restricted diet therapy due to extreme hyperphagia. Many patients experience painful gastrointestinal side

	effects from high dose metformin, which can also deplete vitamin b12, intensifying feelings of fatigue. Several patients describe palpitations and dizziness from blood pressure medications, as well as liver damage and muscular pain from statin use. Patient tolerance and quality of life is continually being tested. All of this leaves patients feeling extremely unwell and struggling to cope. **Many patients have reported that metreleptin has been the only effective treatment for them, allowing them to live a more normal life.** "It is frustrating to know that there is a treatment out there (Metreleptin) but yet I cannot gain it… I was told [by medical experts] that I should be on this treatment… but because I'm in the UK; I cannot have it, it implies that money matters and people don't since Lipodystrophy is rare so why give such an expensive drug to a minority group of population it seems." "We are aware of effective Metreleptin treatment but cannot give it to daughter due to its unavailability"
8. Is there an unmet need for patients with this condition?	There is a significant unmet need for an effective treatment option, which has already been recognised by the committee. Current treatments only work to mitigate the multiple symptoms of lipodystrophy and are commonly considered to be inadequate by the community. No other treatment is available that specifically treats lipodystrophy. Current treatments are restricted in their ability to effectively treat patients due to the highly treatment-resistant nature of lipodystrophy, meaning disease progression and patient outcomes can be severe.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	"I feel in general it helps different aspects of my mental and physical health. If I wasn't on it I think I would have been in hospital more times with pancreatitis, since being on Leptin I have not had one episode." *This patient was previously hospitalised twice with pancreatitis* "Those who respond positively to the treatment will have their one defence against the relentless nature of the disease stripped away. To a healthy person it is hard to understand, but the impact of hunger cannot be overstated. Financially, physically, mentally. Feeling full shouldn't have to feel like a revelation to anyone, especially not to those whose treatment is so heavily dependent on good diet." "Withdrawal of Metreleptin treatment would be a tragedy for many patients who need it. Metreleptin is a lifesaving treatment for many - without leptin, my triglycerides would be through the roof and numerous organs would be full of fat, putting myself at extreme risk. And I am one of the lucky ones. There are other patients who, before Metreleptin treatment, were near death. Metreleptin has saved many lives, and it is critical that patients have access to this lifesaving treatment."

	“Feeling satisfied by food for the first time in my life.”
	“Triglycerides back to normal, appetite back to normal, no more fatty liver”
	“Appetite suppression, stable blood fats, delayed liver deterioration”
	“The hunger issues I had to begin with have improved a lot. I used to be very hungry all the time, even though I had eaten, I would immediately feel hungry again. Now, I don’t get that feeling as strongly anymore. I can now get on without eating more than I need to.”
	“My fatty liver has gone down considerably as when it was first enlarged it was very uncomfortable”
	“It helps keep my weight under control. When I’ve been off the Leptin for a short period of time, I have put weight on and when I have returned to normal use, I find my weight is manageable”
	“Life changing! It allows me more freedom as I no longer have to [inject] huge amounts of Insulin daily. It has kept my weight down so no yo-yoing. It has been very liberating as most of my Lipo health issues have been easily control[ed].”
	“Significant improvements in hyperphagia, immune system, fatty liver, trigl[ycerides] and [Hb]A1C”
	“Diabetes is under control, so I no longer require conventional diabetes medication”
	“Diabetic control is now perfect and requires no diabetic medicine or input. Mixed hyperlipideamia again now within normal limits from being extremely and dangerously high despite medicine and restricted diet. Preventing further fat build up in her coronary arteries, which she could not tolerate. The fat build-up in the chin area has now gone. The constant hunger issue has resolved.”
	“Incredible. My hunger disappeared almost overnight. The fat in my liver reduced by over 75%. My insulin requirements were cut in half”
	[If I could no longer receive leptin] “It would be devastating and my general health would deteriorate, I would be very frightened about my future without Leptin, I believe it has delayed crisis outcomes.”
	“I feel I would have more premature health complications and less likelihood of surviving these complications if I was not on Leptin”
	[If I could no longer receive leptin] “I will revert to being severely resistant to Insulin with all the issues that entails. It will have huge consequences on my physical and mental health as I depend on Leptin to keep me on a positive level and excellent diabetic control.”
	“I am terrified of losing access [to leptin] and going back to constant hunger and being sick 3 out of every 4 weeks. I

	will not be able to maintain my employment." [If I could no longer receive leptin] "The ischemic heart disease would progress further, particularly as the combination of ezetimbe, atorvastatin, bezafibrate and restricted diet was not enough to keep my diabetes and mixed hyperlidaemia under control which in turn would result in my ischemic heart disease progressing further and an early death" [If I could no longer receive leptin] "Absolutely terrified, as the heart disease will worsen, as will the diabetes, hunger, mixed hyperlipideamia. This worry is constantly on our minds" [If I could no longer receive leptin] "My life will be become majorly harder than it already is. My life will be shortened. My mental health will further deteriorate" "I'm terrified of going back to a life without leptin. The hunger is all consuming and incredibly painful" [Struggle with the thought of] "Losing the leptin medicine as this has been the only thing that has given my wife hope and it works!" "We request you to kindly consider our request to provide us Metreleptin treatment. Please" "With a disease I was unaware of until I was diagnosed in 2005 as a 25-year-old it is very daunting. The Leptin offered to me I feel is giving me the best possible outcomes of this disease as there [are] so many ailments that come with it and at different degrees of 'harm' to the body. If I wasn't having the Leptin there trying to maintain a balance in my health, I think I would be more unwell than I have been." "Leptin has been the ONLY drug that has enabled me to control my severe [insulin] resistance and have a normal life." "I hope that the medical field starts to recognise how hard lipo is to live with, and that if there is a medication that might help people with our condition, it should be available to the people who need it" "Metreleptin changed my life. I cannot imagine how I managed 37 years in the world I was living. No human should have that hunger. My body functions so much better with treatment. I fear I will die without it." "metreleptin therapy is extremely important to me as it has allowed me to lead a somewhat normal life and the withdrawal of this treatment will be devastating to not only me but also my family as [it] will mean that my health will start to deteriorate and they will have to watch knowing that there is nothing that they can do to help." "metreleptin was an absolute lifeline and the difference it has made to us is incredible and to think about losing it is devastating to us. [Losing leptin] puts us in an unimaginable position and one we do not want to happen."

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Of the 30 survey respondents, not one discussed any disadvantages of the technology. There are very few side effects of the treatment; some patients have previously reported disadvantages relating to the need for daily injections and injection site irritation. However, these are frequently minor concerns that are far outweighed by the metabolic advantages. There are some studies reporting development of sensitizing antibodies. However, Lipodystrophy UK has had no contact with any patient experiencing this rare side effect. Effectively, the only discussed disadvantages raised by survey participants were either currently being unable to access metreleptin treatment (where eligible), or the fear of its withdrawal if it is not made available on the NHS.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with generalised lipodystrophy have a total lack of subcutaneous fat and therefore experience the most severe (and earliest onset) manifestations of metabolic disease. All untreated CGL patients would hugely benefit from metreleptin treatment, with the earliest possible intervention. The majority of partial lipodystrophy patients would also benefit massively from intervention with metreleptin. While the manifestations of metabolic disease are generally less severe than for metreleptin untreated CGL patients, metreleptin untreated FPLD patients will often experience more severe manifestations of metabolic disease than metreleptin treated CGL patients. There is a small subset of partial patients who would not benefit from this treatment, but the Severe Insulin Resistance Service team at Addenbrooke's may easily stratify these.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We are not aware of any equality issues.
Other issues	
13. Are there any other issues that you would like the committee to consider?	In such a small patient community, the cost of the treatment dwarfs in comparison to the lifelong treatment of chronic and acute medical emergencies. Metreleptin is the only therapy available to directly treat lipodystrophy, and patients deserve health equality in treatment. Lipodystrophy UK recognises that metreleptin has some limitations including, at this point, a lack of long-term data

	and treatment comparison studies. We also anticipate that, as a treatment for an ultra-rare disease, demonstrating value for money may be a challenge. We would urge NICE, NHS England and Amryt to find a solution that achieves both access and affordability and that is a fair reflection of metreleptin's value. It is critical that NICE can be flexible in considering both the available evidence and the additional benefits / pertinent contextual issues. Alongside this, it is vital that metreleptin is appropriately priced according to its value.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Lipodystrophy is debilitating, life-limiting disease, with far-reaching comorbidities that significantly impact the quality of life of patients and their families
- Metreleptin is a specific treatment for leptin deficiency in lipodystrophy patients who are extremely resistant to conventional diabetes/lipid lowering therapies
- There is evidence from trials that metreleptin is efficacious in patients with lipodystrophy and this has been confirmed by the positive opinion from the EMA/FDA/Japanese regulators, as well as the patient experience data reported in this submission
- Quality of life/life expectancy has been shown (here and elsewhere) to be improved by a reduction in metabolic complications, attributed to metreleptin therapy
- Patients currently on treatment are not being funded via the NHS – Amryt is providing the drug free of charge to a very limited number of patients on compassionate grounds. Without an agreement to fund metreleptin via the NHS, all patients will be withdrawn from treatment. Withdrawal of therapy from patients currently taking metreleptin and denial of therapy for patients deemed likely to benefit by specialist clinicians, especially young children, is unethical and would be devastating to the patient community

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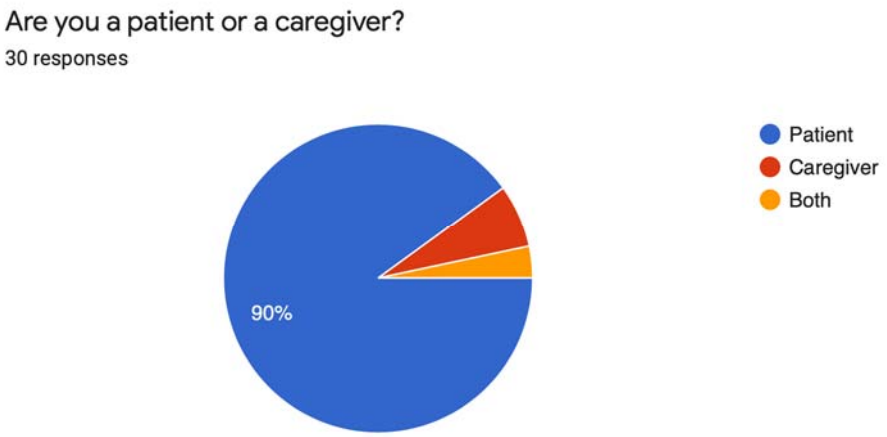
Living with Lipodystrophy – A Community Survey

Developed and collated by Lipodystrophy UK, 2020

All survey responses are reproduced, without editing, except for the removal of blank responses.



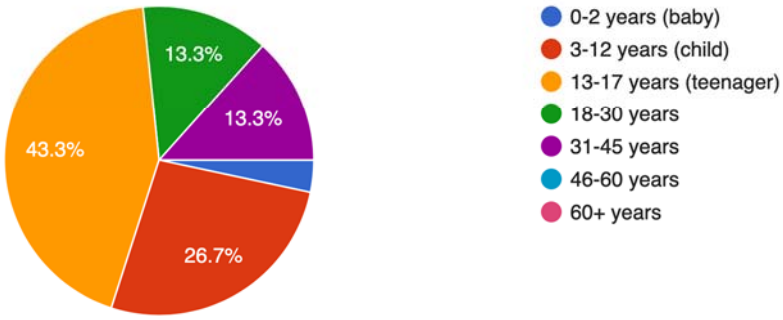
What is your/the patients' lipodystrophy diagnosis?

Familial lipodystrophy type 3
Partial Lipodystrophy type 3
Familial Partial Lipodystrophy type 3
Atypical progeroid
Congenital lipodystrophy Berardineli Seip's Syndrome
FPLD type1
Familial Partial fpl3
FPLD type 1 - Kobberling's
Partial lipodystrophy (dunnigan)
Partial lipodystrophy
Partial Lipodystrophy
Familial partial Lipodystrophy
Acquired partial lipodystrophy
Facial Partial Lipodystrophy Type 2 Secondary to A-LMMA Mutation
Familial Partial Lipodystrophy mutation in PPARRA Gamma

PFLD
Familial Partial Lipodystrophy
Partial lipodystrophy
Familial partial Dunnigan type
Type 2 partial lipodystrophy
Partial lipodystrophy
FPLD
Familiar partial
Familial Partial Lipodystrophy type 2
Familial Partial Lipodystrophy Type 2
Familial Partial Lipodystrophy
Acquired generalised lipodystrophy
Lipodystrophy
Partial Lipodystrophy
FPLD2

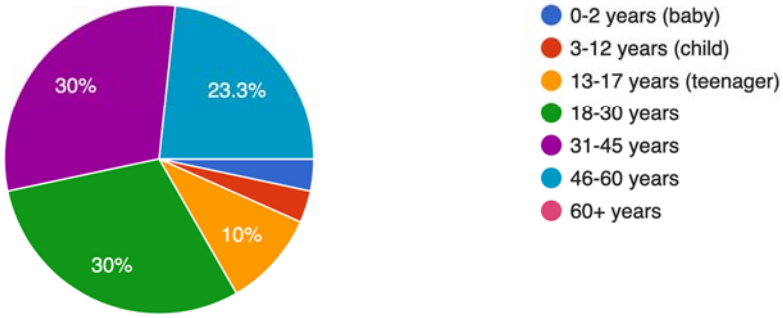
How old were you/the patient when you/they first had symptoms?

30 responses



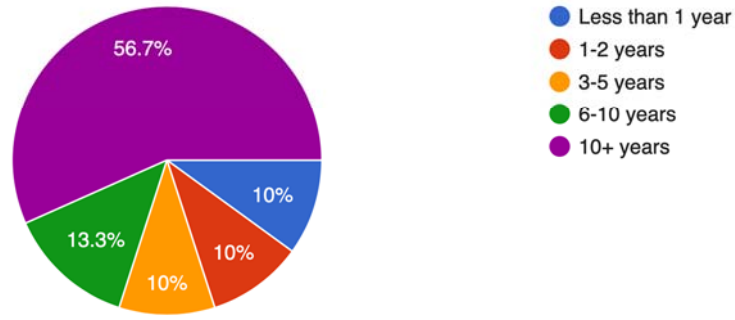
How old were you/the patient when you/they were diagnosed with lipodystrophy?

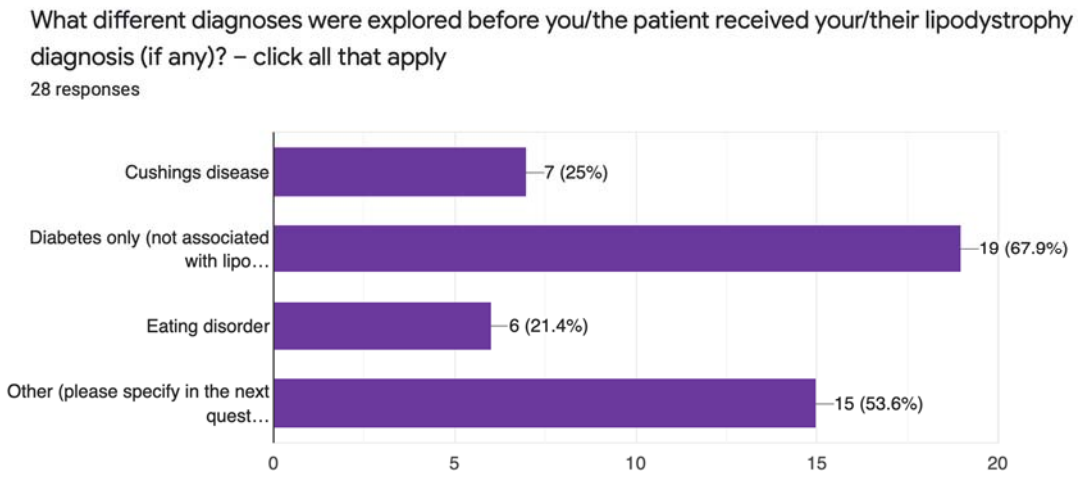
30 responses



How long between symptoms and diagnosis?

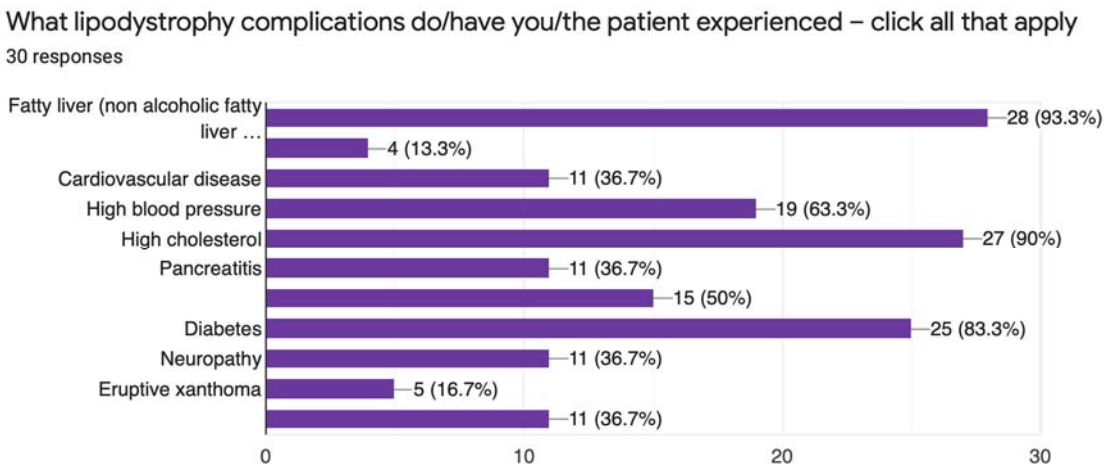
30 responses





Please specify any other diagnoses you/the patient received

Severe Insulin Diabetes
All kinds of things. Mental illness was also a big issue
I had a heart attack at 42 (2008) and all symptoms were put down to heart disease/palpitations/unstable angina
Cinns syndrome
Depression, anxiety, crohn's, nafld, htn, pcos
Fibromyaglia
Heart disease , poly cystic ovaries , generally not looking after self , have a tummy tuck !
Alcoholic Liver Disease (i am tee total), Pancreatitis, Hypothyroidism, Polycystic Ovarian Syndrome, Mixed hyperlipidaemia, Myotonia Congenita, Hypertension, Obesity
Diabetes, Obesity, NASH (originally alcohol related), Myotonia congenita, polycystic ovarian syndrome, pancreatitis, hypertension, mixed hyper lipideamia and hypothyroidism.
Fatigue, And loss of body fat yeah
I was fortunate to be diagnosed quite quickly, as my endocrinologist had heard of lipodystrophy and was in contact with the Cambridge team from the beginning



Please specify any other complications you/the patient do/have experienced

Excessive hair growth, very high testosterone, I get chronic muscle pain in my legs, i have rheumatoid arthritis and suffer badly in my hands. I don't have periods.
Recurring UTI, tiredness, hunger, cramps, anxiety
Carpal tunnel in both wrists
Skin discolouration ,servers carpet tunnel and leg cramps
Coccyx pain, knee pain
Extreme fatigue, list of body fat. Very high sugar levels.
No warning regarding Hypos, Neuropathy in hands and feet, stroke, retinopathy, podiatry problems
Very high triglycerides, gallbladder failure, sleep anpnea
Gastroparesis
Nausea, fatigue, body aches and pains constant, underactive thyroid/fibromyalgia/heart palpitations
Hyperphagia, low immunity, asthma, allergies, muscle spasms, migraines, heart intolerance, cold intolerance, multiple cases of childhood pneumonia, scoliosis, disc degeneration, angina, tachycardia, sleep apnea
Not being listened to , lose of confidence, feeling a freak
Angina, NSTEMI x 2, CABG x 5, Stents x5 Hysterectomy and bilateral salpingooophrectomy Removal of sternal wires due to extreme pain and wires protruding though skin due to lack of subcutaneous fat Abdominal pain, joint pain, extreme hunger/always hungry, extreme tiredness, Depression, problems sleeping. Despite other family members receiving the diagnosis of FPLD2, I was ignored when alerting local doctors to this and because they had not heard of it I was dismissed as not knowing what I was talking about. Diagnosed as an alcoholic even though I have been teetotal for years and accused of lying by the doctor.
Angina, menorrhagia, extreme tiredness, extreme hunger (constantly), hypotrophic muscles, muscle tears and muscle cramps.
Cardiac and Respiratory issues Lipoatrophic Diabetes Non-alcoholic Fatty Liver Disease (NAFLD) Splenomegaly Kidney Disorder Gastroparesis Exocrine pancreatic insufficiency (EPI) Vitamin Insufficiency

Hypogonadism Aches & Pains Chronic Fatigue Anxiety & Depression
Insulin resistance Extreme fatigue Joint pain through loss of fat pads
Appendicitis removed and gallbladder removed
Suspected IBS, due to the impact of metformin over many years

Please give details of the complications you/the patient do/have experienced

A short while before I was diagnosed with Lipodystrophy I was hospitalised with dangerously high triglycerides, eruptive xanthomas, uncontrollable diabetes, extremely high blood pressure and an irregular heartbeat / tachycardia. I was at high risk of getting pancreatitis. Since then I have a daily battle to keep all of these conditions in check to prevent more serious consequences such as a stroke or a heart attack. I take 8 tablets a day, at just the age of 31, to help manage these conditions.
High triglycerides, apparent generalized loss of fat
Liver fibrosis
At 37 had to have a quadruple heart bypass
I can not sit on certain chairs or for very long due to the fat not being on my bottom.
Huge amounts of insulin required before I trialled Leptin
Hyperphagia, low immunity, asthma, allergies, muscle spasms, migraines, heart intolerance, cold intolerance, multiple cases of childhood pneumonia, scoliosis, disc degeneration, angina, tachycardia, chronic fatigue, anxiety, depression
Tender soles of feet. Legions on liver. Diabetes. Weight gain.
Heart bypass
Angina diagnosed initially as indigestion and treated with lansoprazole. CABG x 5, stents x 5 (6 months after the CABG due to the progression of the ischemic heart disease) Complications during CABG surgery resulting in 1 week on ECMO
Cabg X 5, Stents X 5 (6 months after Cabg X 5), hysterectomy and removal of sternal wires, due to protrusion through skin.
I have a genetic condition called Atypical Progeroid Syndrome (APS) characterised by a mutation in the LMNA gene and is a combination with Familial Partial Lipodystrophy (FPLD), This is characterized by ectopic fat accumulation, due to insufficient storage capacity of subcutaneous adipose tissue, thus leads to severe insulin resistance (IR), often manifesting by acanthosis nigricans, type 2 diabetes mellitus (T2DM), hyperlipidemia, nonalcoholic fatty liver disease (NAFLD) along with several other subconditions . The condition results in multiple organ malfunction and difficulties in day-to-day living. FPLD affects each organ as fat builds up within those vital organs such as kidneys, liver, heart and in other parts of the body, this is due to the fat cells that have decayed overtime. I tharefore not only have multiple organ dysfunction but also am very thin in appearance. My fat percentage overall is significantly below average meaning that several other complications arise such as not being able to find suitable clothing/footwear that limits discomfort. Cardiac and Respiratory issues: I have a heart condition that is characterised by a narrow mitral valve that is dilated, additionally there is fat build up which results in difficulties in breathing, heart murmur, rapid heartbeat and other heart-related symptoms. Mobility is hence limited as I get very short of breath during walking and whilst carrying out any form of physical activities, this affects my ability to carry out tasks like cleaning/cooking and all other household chores. As I have issues with my resiratory system, it results in further breathing problems such as Sleep Apnea. This is caused by a lack of oxygen being passed down into the lungs during sleep which means that my breathing level is very low. As my oxygen level is low, I use a CPAP mask during sleep which is aimed to help breathe overnight. I however wake-up often gasping for breath and feel significantly fatigued. Lipoatrophic Diabetes: Due to APS & FPLD I have a specific diabetes that requres daily monitor, as sugar level fluctuates rapidly

depending on diet and as part of FPLD. I therefore have to check my diabetes before and after each meal and alter my diet accordingly.

Dietary Requirements:
As FPLD is linked to fat wasting that causes other issues, I am on a very low carb, low fat, low cholesterol & medium protein diet, though appearance-wise I am very slim, I am obese internally as fat builds up within organs and not around the outside. The specific diet is said to slow down rapid fat build up that is caused by unhealthy eating.

Non-alcoholic Fatty Liver Disease (NAFLD):
This is caused by an excess build up of fat in the liver that is not alcohol-caused issue & so is common in those with FPLD. The liver therefore is damaged and inflammated. Due to this I suffer from frequent increased abdominal pain, loss of appetite, more weight loss and weakness. ,

Splenomegaly:
This is a condition that occurs when the spleen becomes enlarged. As our spleen is a part of our lymphatic system. It strengthens the immune system by storing white blood cells, helping in the creation of antibodies. Since my spleen is enlarged, I am more prone to catching infections and viruses as my body produces less white blood cells that are need to fight infections/virals. This tends to worsen during winters as I easily get flu and other virals which my body struggles to fight from. The vital infections I get mainly lasts longer than an average person, this for me is up to 4 weeks.

Kidney Disorder
Fat build up in the kidneys has meant that my kidneys are weaker thus I tend to need the mens room several times in a day, as my kidneys are unable to retain fluids. Additionally, i get very thursty and require water frequently throughout the day.

Gastroparesis:
This is where the stomach cannot empty itself in the normal way, food therefore passes through the stomach slower than usual. This leads to various difficulties as I am not able to eat without feeling sick and so vomit & am nauseas. Upon eating a small amount, I get full immediately which then causes severe abdominal pain and sickness. I hence do not get enough nutrients needed to function properly, thus as a way to limit discomfort & abdominal pain I tend to stay more on liquids, meal replacements (Ensure) and light solid foods such as soups. This however, still means that I get nauseous even by consuming only liquids at times but it alleviates intense pain that I get if eaten a full meal (which is very rare now). Thus food consumption of any type results in vomiting, nausea & sickness. On days when I am able to eat more solids, I get increased bloating & indigestion as a consequence since my body struggles to store & process food. .

Exocrine Pancreatic Insufficiency (EPI):
This is the inability to properly digest food due to a lack of digestive enzymes made by the pancreas. The main issues faced are maldigestion and malnutrition, associated with low circulating levels of micronutrients, fat-soluble vitamins and lipoproteins. Due to this, I get daily episodes of diarrhoea, indigestion, abdominal pain & cramps.

Vitamin Insufficiency
As I am unable to consume food properly, I therefore suffer from a deficiency in Vitamins such as Vitamin D, this means that I have to take supplements to overcome the insufficiency which are linked to several other health problems.

Hypogonadism
This is a syndrome characterized by the presence of low testosterone levels. This has led to decreased libido, impaired erectile function, muscle weakness, increased adiposity, fluctuating mood and decreased vitality. The low level of testostrone produced in my body has also led to the development of chronic fatigue, though FPLD already causes chronic fatigue but it is even worsened due to low testostrone. I therefore am on Testostrone Replacement Therapy every two weeks, this is to give the body a decent level of testostrone men require. However, there are sone side effects of this therapy which for me are increased tiredness for up to 3 days, excessive sweating, low mood and muscle ache.

Aches & Pains
I get muscle & joint pains daily due to less fat on my body, my feet get very sore as there is less padding underneath thus is painful when standing and walking, I also get stiff joints meaning that it causes discomfort.

Additionally, I get occassional headaches.

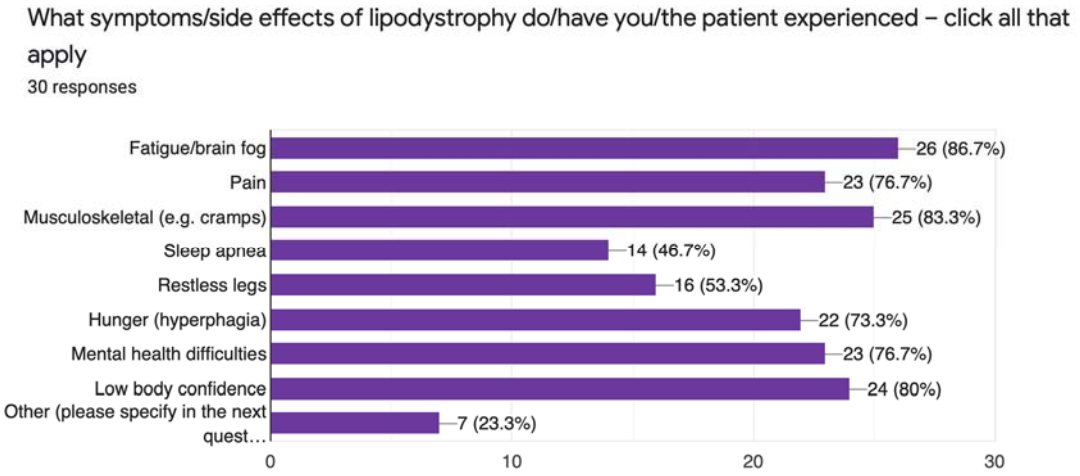
Chronic Fatigue
Due to this, I am extremely tired and lo on energy. I tend to sleep long hours, often 15-18 hours a day & still feel exhausted. This takes a toll on my day-to-day routine as I have difficulties carrying out tasks since I am just too fatigued.

Anxiety & Depression
I suffer from episodes of low mood, depression and anxiety. This is due to the trauma and ill-treatment i have suffered, additionally it is a side effect of my Testostrone Replacement Therapy. .

Extreme fatigue
Joint pain
Extreme hunger
Uncontrollable diabetes
Pancreatitis

Appendicitis removed and gallbladder removed

On an insulin pump due to high insulin demands. Had my gall bladder removed due to high fat and gall stones



Please specify any other symptoms/side effects of lipodystrophy you/the patient do/have experienced

Suffer with chronic leg pains.

Heart palpitations

Pain in feet, low confidence levels and irritability

Low Vitamin D/ Magnesium

Low self esteem

Body Dysmorphia

LACK OF ENERGY / STAMINA

My life is effected every day. When you have insulin resistance and diabetes, I feel like your body is constantly trying to correct all the issues, and it creates a constant state of not feeling well, ever.

Legs feeling like are going to explode with varicose veins

Always cold or hot

Lack of awareness by medical professionals

Lack of confidence overall. Teased and picked on all my life due to my appearance

Constant comments of my appearance, depression and as above

Aches & Pains
Chronic Fatigue
Anxiety & Depression
Nausea
Diarrhoea
Acid Reflux
Sleep Disturbances (Insomnia & Increased Sleep)

Loss body fat. Always feeling tired

Bloating

Please give details of the symptoms/side effects of lipodystrophy you/the patient do/have experienced

I experience a high level of discomfort every day. The smallest tasks causes body pains that are equivalent to the pain you get after a weight training session. For example, if I carry bags of shopping, the next day my arm muscles would be painful and would shake even if I tried to lift something light up. Just recently, i've struggled with knitting as it causes pain in my hands.
Other than the pain, the brain fog and fatigue are the worst for me. I find it unbelievably hard to cope and function. I'm starting to notice a decline in my work performance, despite me trying my best to overcome it or work extra to compensate. I fear I will lose my job over it. All of this causes me to live in constant anxiety and low mood.
The hunger is a cruel part of this disease, I know I shouldn't eat much for my health. But when your mood is low, you feel rubbish about yourself and you genuinely feel really hungry, it's extremely hard to go ahead how you feel.

Abdominal pain from damaged liver

Body image issues people pointing out you look muscular for a female can be upsetting when it's not something you have intended to do it's out of your control

Lack of energy / stamina
chronic fatigue

Time off work, extreme fatigue, vomiting, headaches, loss of balance.

Depression, extreme hunger, tiredness, lack of concentration, forgetfulness, muscle cramps, constant worry about the progression of the severe ischemic cardiovascular disease.

Cardio problems as listed, following a very low fat/carb/protein diet, memory issues, tiredness, pins and needles.

Aches & Pains
I get muscle & joint pains daily due to less fat on my body, my feet get very sore as there is less padding underneath thus is painful when standing and walking, I also get stiff joints meaning that it causes discomfort. Additionally, I get occassional headaches.

Chronic Fatigue
Due to this, I am extremely tired and lo on energy. I tend to sleep long hours, often 15-18 hours a day & still feel exhausted. This takes a toll on my day-to-day routine as I have difficulties carrying out tasks since I am just too fatigued.

Anxiety & Depression
I suffer from episodes of low mood, depression and anxiety. This is due to the trauma and ill-treatment i have suffered, additionally it is a side effect of my Testostrone Replacement Therapy.

Nausea
I get daily episodes of nausea which restricts me from eating fr long hours, sometimes the whole day. This causes discomfort as well as hunger pains if not eaten for more than 4 hours.

Sleep Disturbances
As I get tired fairly easily and quickly I sleep up to 12-14 hours a day, sometimes even longer or no sleep at all. My sleep is also affected by pains and other symptoms which restricts my ability to have a regular sleep pattern with a decent quality of sleep.

Always feeling tired

Extreme fatigue severely affects my every waking moment. I suffer a lot of pain, mainly related to muscle tension (particularly back, calf and tension headaches) and gastrointestinal.

Describe the pain/abdominal pain that you/the patient live with on a daily basis (if applicable)

I suffer everyday with pain, I take pre-gablin to try and manage my pain. I struggle with work so much as the pains I get are ridiculous sometimes. I have a good day then the next two are bad for me.
I live with muscle pain. This is generally all over but is worst in my legs and back. It can make daily tasks more difficult, such as carrying things.
Muscular aches and tightness. Nerve pain in feet.
Pain in feet and abdomen
Bouts of pain sometimes causing vomiting related to diet, unable to sleep on my right hand side when inflamed
Pain in my intercostal muscles in my rib cage, if I move suddenly or reach for something muscle spasms which are incredibly painful and go rigid so I have to stop and slowly walk around rubbing the area until the worst stops! It's like having a pulled muscle every day!
Constant bloating, extreme flatulance that's difficult to get rid of sometimes can feel intestinal cramping and general feeling of nausea
High pain in the joints and legs.
Mostly joint and muscular pain
Bloating becomes painful
My body hurts ALL the time. My hands fall asleep all the time. I can't walk or stand for long, because I have no fat on my feet. My back and hips hurt all the time. I have constant, contentious bloating and abdominal pain.
Nausea, intestinal cramps, stomach cramps, and uterine cramps
Some days on a scale of 1-10 - between a 5 & 8 (terrible bloating)
Joint and muscle pain on a daily basis.
Muscle pain. Fatigue. Liver pain.
The joints in my hands, my back (particularly the coxis) & legs muscles are very painful every day
Cramping pain
Abdominal cramps constantly
I get moderate abdominal pain resulting in severe discomfort and inability to eat for long hours till the pain subsides. This is a major challenge as Lipodystrophy causes frequent and severe hunger which is difficult to control especially if suffering abdominal pain. In addition to this, I get pain in my muscles, joints and limbs meaning that I am unable to carry out even the simpler tasks on a daily basis depending on severity of pain. Furthermore, my feet and legs get extremely sore due to walking even short distances as there is very little fat (padding) which is required to protect our feet from hard surfaces. I also get occasional headaches which demand rest.
Pain in upper abdomen Bloating
Really bad craps painful sools of feet aching arms and burning calfs soar really painful buttocks
Fatigue
I can get severe stomach pains, diarrhea and bloating. I suspect this is due to IBS brought on by the torment on my system of metformin side effects experienced for many many years

What treatments/medications do you/the patient currently receive (please also indicate for which complication they have been prescribed)?

Metformin, trazodone, steroids, hydrochloriquine, pre-gablin, atrovastatin. Folic acid.
Labetalol x2 a day - high blood pressure

Metformin x4 a day - diabetes Atorvastatin x 1 a day - high cholesterol trimethoprim x 1 a day - chronic infection
Humulin R U500 insulin, Toujeo U300 insulin and metformin for diabetes. Omacor for high cholesterol (currently taking a break from Bezafibrate and Rosuvastatin as pregnant) Gabapentin for neuropathy, Venlafaxine for anxiety and depression. I was on metraleptin but stopped due to pregnancy. I also take levothyroxine for congenital hypothyroidism.
Metfirmin tablet (1500mg per day) for diabetes and Envas for kidneys
Just anxiety medications
Metformin, Jardiance- Diabetes Omeprazole- gastric Citalopram- depression Losartan Amlodipine- Hypertension Atorvastatin Hypertension Amitriptyline- pain Leptin- Fpl
Fenofibrates to lower my lipid levels Metformin to help keep diabetes at bay Antox to help my pancreas repair itself Pioglitazone to help keep diabetes at bay Orlistat- to take out any fat from what I eat Vitamin D as Lipo strips my levels
Diabetes - Metformin, sitagliptin, empagliflozin Heart - atorvastatin, aspirin, furosemide, bisoprolol, gemfibrozil Blood pressure - ramipril Stomach - lansoprazole
Insulin and diabetes tablets many different ones high cholesterol blood pressure vitamin D and the pill
High levels of insulin injection
Fenofibrate - for high cholesterol control 4 different tablets to control hypertension metformin for diabetes control
Leptin- severe insulin resistance Networking- Diabetes Levemir Insulin Novorapid Insulin Amitriptyline - Neuropathy Levothyroxine - Thyroid Aspirin - Stroke Seryraline - Depression
I take 2 diabetic medications, meds to help with lowering my blood pressure, cholesterol, triglycerides, gabapentin, antianxiety meds. I see an endocrinologist once every 3 months. I go to NIH once a year. I do 20 minutes of yoga a day. I use a low fat, low sugar, higher carb diet.
Levothyroxine, Humalin R U500, Metformin, meloxicam
Medication for heart disease/palpitation/unstable angina/diabetes/underactive thyroid/neuropathy/depression/anti-nausea medication/pain relief
Lisinopril, low calories/high exercise, b12, vit d, fish oil
Metreleptin-lipodystrophy, metoprolol-high blood pressure, venlafaxine-muscle spasms and anxiety, zyrtec-allergies
Suralip. Artovastatin. Both for cholesterol. Humolog and tresiba for diabetes. Amptripline and duluxetine. Both for pain and mental health.
Metformin-pre diabetic Propranolol-for migraine Furosemide-for swelling/water retention Atorvastatin-for cholesterol
Heart meds , lipid meds , diabetes meds , insulin
Aspirin 75mg OD life long Levothyroxine 75mcg OD for hypothyroidism Ezetimbe 10mg OD for mixed hyperlipidaemia Myalepta (Metreleptin) 0.5ml OD artifical replacement for low leptin levels and diabetes Lanzoprazole 30mg BD for abdominal pain/indigestion/aspirin Atorvastatin 80mg OD for mixed hyperlipidaemia Isosorbide MR 60mg OD for angina/ischemic heart disease Carvedilol 12.5mg BD for hypertenison/ischaemic heart disease

Ramipril 1.25mg BD for hypertenison/ischaemic heart disease
Ranolazine 750mg BD for angina/ischemic heart disease
Bezafibrate 400mg OD for mixed hyperlipidaemia
Walnut Oil 2mls OD for low minerals etc in body
Vitamin D 25mcg alternate days due to low vitamin D levels
GTN Spray as required for Angina

Aspirin Cardio issues
Levothyroxine hypothroidism
Ezetimbe mixed hyper lipidemia
Myalepta (Metreleptin) Lipodystrophy (low leptin level)
Lanzoprazole Gastric problems (taking aspirin)
Atorvastatin mixed hyper lipidemia
Isosorbide MR ischaemic heart disease and angina
Carvedilol hypertension and ischaemic heart disease
Ramipril hypertension and ischaemic heart disease
Ranolazine ischaemic heart disease and angina
Bezafibrate mixed hyper lipidemia
Walnut Oil low levels of essential minerals
Vitamin D Low vitamin D level
GTN Spray Angina

Exocrine Pancreatic Insufficiency (EPI)
Creon 25000 gastro-resistant capsules (Mylan) - 6 capsules with meals, 2 with snacks.

Nausea and Sickness
Domperidone 10mg tablets - One To Be Taken Up To Three Times A Day. Maximum 3 In 24 Hours

Meal Replacement
Ensure Plus milkshake-style liquid - One carton twice a day.

Diabetes
Gliclazide 40mg tablets - One To Be Taken Daily

Diarrhoea
Loperamide 2mg capsules - Two To Be Taken Immediately Then One To Be Taken After Each Loose Motion

Sleep limiting tablet
Modafinil 100mg tablets - One To Be Taken Each Morning And One To Be Taken At Lunchtime

Diabetes
Pioglitazone 45mg tablets - One To Be Taken Each Day

Kidney Disease
Ramipril 5mg capsules - Take One Twice Daily

Acid Reflux
Ranitidine 150mg tablets - One To Be Taken Twice A Day As Needed

Testosterone Replacement Therapy
Sustanon 250mg/1ml solution for injection ampoules (Aspen Pharma Trading Ltd) - For IM injection every two weeks by practice nurse
Therapy.

Leptin-hunger
High cholesterol- rosouvastatin and fenafibrate
Kidney issues- ramapril
Pains- co codimol

Just pain killers diaydrocodnie

Take no medication

Atorvastatin - high cholesterol
Ezetimibe - high cholesterol
Amlodipine - high blood pressure
Losartan - high blood pressure

Metformin - diabetes/PCOS Insulin - diabetes Leptin - lipodystrophy Targinact - restless legs Trazodone - restless legs/fatigue Sertraline - depression Vitamin D - deficient

Do you restrict your/the patients' diet in any way? For example, restricted fat diet, low carb diet, restricted calorie diet. Please give details

Try to eat less sugar and lots of fruit and vegetables.
I generally do a reduced carb and low fat diet
Reduced fat and refined sugars as mich as tolerable.
No
Low fat and no sugar diet
Low carb, high protein
Low fat and carbs
Low fat/ low sugar diet
Low fat diet with small portions regularly throughout day rather than 3 big meals
Low fat / limit carbs
I try, I never fry anything. But I crave bread and sometimes can eat anything I can get my hands on.
Low carb
I try to eat a low-fat diet but often struggle with this
Low Fat and Sugar
I try to eat under 20 grams of fat a day, due to chronic pancreatitis. I also try to limit my sugars.
Try to eat low fat and low carb
Not to a great extent, restricted fat/mostly white meat/low sugar
Yes, far, carbs sugar, calorued
I am plant based, try to restrict calories
Yes. I do not eat any grains and focus on a keto diet with healthy fats as the primary source of energy.
Try to follow a low fat diet
Low fat diet , try to burn 3000 +calories a day , but only eat 1800
Restricted fat 30mg per day , restricted carbs 12 portions per day, restricted protein 65mg per day
Yes, low fat (30g/day), low Carbs (12 portions/day) and low protein (65g/day)
Yes, as Lipodystrophy is a fat wasting disorder having a healthy and monitored diet is crucial. I am advised to consume food that is high in protein, low in carbs and low in sugars and fats. This is very challenging as most foods contain some form of fat and sugars hence I have to calculate my daily calorie and fat percentage. It is extremely difficult as I cannot order a takeaway or eat out since
Low fat low carb diet
Low fat and low carbs
No restriction on the diet
Low fat, low carb

How many episodes of pancreatitis have you/the patient experienced?

None
0
1 suspected plus 4 confirmed
0
Not aware
0
One proven others not hospitalised
2 episodes where I have been hospitalised and 4 mild episodes where I just stopped eating and just drank fluids for a week at a time

Twice before I was diagnosed FPLD
None
1
None
N/A
0
I have had over 25 episodes. I have had a plasmapherisis due to pancreatitis.
0
Not sure that I have
3

2-5
0
None
None
None
9
Approximately 9
0
8+
0
None
0

How old were you/the patient when you/they had your/their first pancreatitis attack?

21	21	25	35
40	37	19	16
49 years old	25	35	

How many times have you/the patient been hospitalised because of pancreatitis?

0	Twice	No	Once
4	1	3	1
1	None	1	5
Twice	4 or 5	Nil	

Have you/the patient been hospitalised for anything lipodystrophy related in the last 12 months? Please give details

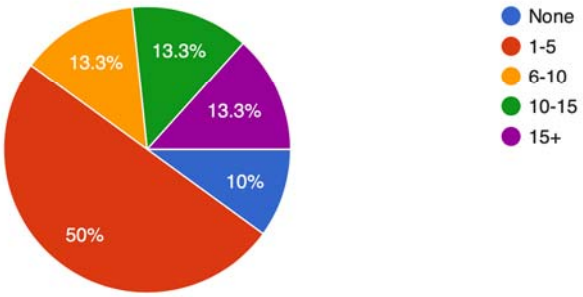
Attended A&E for Bell's palsy but whether this is directly LD related is unknown
No
Not hospitalised but we do regular followup
No due liver consultant appointment and liver scan delyed
No
No
Never
None
No

No
Several Hypos (blood sugar at 1)
I had a hysterectomy, tube and right ovary removed because of PCOS. I had a growing, changing mass on my right ovary.
No
No
No, I won't go to the hospital anymore
No
No
No

No	No
No	No
N/A	No
No	

How many outpatient appointments and/or GP appointments related to lipodystrophy have you/the patient had in the last 12 months? Please give details in the next question

30 responses



Please give details of your/the patients' outpatient appointments and/or GP appointments related to lipodystrophy over the last 12 months (if applicable)

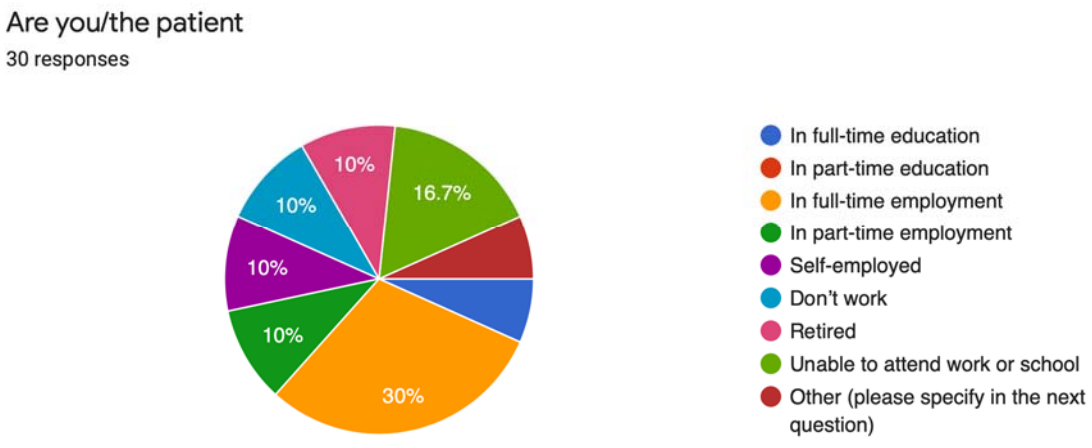
I had a annual review with dr steers, I can't remember the outcome.
Investigation for sleep apnea Cardiology appointments (more than one, including scan) High blood pressure investigations Liver MRI Diabetes review Lipid clinic Various blood tests, checking things like my cholesterol & diabetes Kidney scan Appointment for reoccurring infection in my bladder
Increased amount of monitoring and appointments with consultants due to prenatal planning and current pregnancy. I currently have fortnightly appointments with endocrinologist and 6 monthly appointments with lipidologist.
It was just a check in; I have an appointment with an endocrinologist once every six months
Every 2 to 3 months visit to doctor
Addenbrookes
Annual review at Addenbrookes severe insulin Resistance service. Diabetic consultant local.Diabetic eye screening. Awaiting Liver consult delyed
CAMBRIDGE Addenbrooke hospital - yearly appt - sent me for appt for MRI liver- appt for angiogram to check heart - sent me appt for echocardiogram Hammersmith hospital - liver specialist At Mary's Paddington - Lipid Clinic Was supposed to have a further 3 appts which have been deferred/cancelled due to lockdown
See one of the main doctors talk about any ongoing issues and any new ones there is usually a diabetes nurse there who is helpful in getting you to understand what works treatment wise for the diabetes side of things for me. It won't always be the same for everyone. They educate you so you can manage your diabetes with more ease.
All endocrine appointment
Blood tests ultra-sound to check liver

endoscopy to check for varices associated with liver cirrhosis
Endocrine Consultant Severe Insulin Resistance @ Addenbrooks Hospital Neuropthalmology @ Charing X Hospital Atypical Diabetes Clinic at St Mary's Hospital Diabetic Specialist GP Various ultrasounds/MRI Opthalmology @ St Mary's
Regular endo check up. GP has seen me for tendonitis and walking pneumonia
Endocrinologist, diabetes management, psychologist
[redacted] and [redacted] at the Lipid Clinic at the Royal Free London
I avoid going to doctors
Metreleptin and diet keep my health in check so I only go in for check-ups
Liver mri, ultrasound.
Cambridge - SIR clinic & general LD check up x2 St Thomas - cardiac check up x2 Local hospital - arthritis scans/appointments x2 Kings - neurology x1
Insulin resistance clinic , cardiologist clinic , lipid clinic , liver clinic and scans , dermatologist clinic and rhemutoid clinic
Appointment at Addenbrookes with Severe Insulin resistant service to review Lipodystrophy Telephone appointment with Addenbrookes with Severe Insulin resistant service to review Lipodystrophy. Cardiology OPD Appointment for heart disease, Pain clinic appointments for leg pain, GP appointments for diabetes f/up and bloods, liver scan results, leg pain, abdominal pain, Hospital appointment for ultrasound of liver
Appointment with [redacted] at Addenbrooks hospital in Cambridge Telephone appointment with [redacted] at Addenbrooks hospital in Cambridge Pain clinic appointments X 8 at Beverley hospital Ultra sound appointment for liver ultra sound at Beverley hospital Physiotherapy appointments X 2 at Hull Royal Infirmary for shoulder mobility issues GP appointments X 8 for blood tests, stomach problems, diabetes review and shoulder issues
I am under regular examinations for most of my conditions but mainly for diabetes, Endocrinology and Cardiac issues. Since not all my conditions can be monitored or is understood by medical professionals. Hence I get outpatient appointments for various tests such as MRI, X-Ray and other tests depending on symptoms. Additionally, I am under the care of a diabetes clinic who monitor my blood sugars and carry out screenings.
Addenbrookes- lipodystrophy and insulin resistance Diabetes clinic Gp- bloods and health check up Rheumotology- pains
None
Addenbrooke's specialist clinic, local diabetes clinic, fertility-based appointments, annual GP review, sleep clinic

What impact did/does lipodystrophy have on your/the patients' ability to perform at school/work?

I struggle a lot with work but I feel no one understands when I say I'm struggling or in pain as I'm only 27 and should be 'fit and healthy'
It is greatly affecting me. I work in a fast paced role as a web developer and am required to create complex digital platforms. The brain fog and fatigue are hindering me so badly, and getting progressively worse, that I fear the day will come when I lose my job. I have always been a hard worker, have never been fired from any role, so when that day comes it will be extremely upsetting.
Fatigue and pain forced me to give up work in 2012. Attempted to return to work in 2015 unsuccessfully due to LD symptoms and depression.
None

Low confidence and poor performance at school
I work full time but then spend weekends sleeping to recover. Had high level of sickness
Not working retired through Ill health exhaustion, pain and digestive issues
When I get cramps or spasms I have to go and take a walk to help reduce the pain which can happen several times a day so I am not at my desk! I have even had to leave a meeting due to this
I work as a post person I'm walking for several hours so after many years I now find my legs ache even with rest and massage the aching doesn't go away my feet hurt as there is no cushioning on the soles of my feet, I also have restless leg syndrome that affects my sleep so I can feel quite fatigued
I dont work due to another disability, but because of the low confidence I have with how I look I dont go out.
Extreme tiredness constantly
I gave up work in 2009 as the fatigue simply beat me - my quality of life was poor
My hours have been reduced re extreme fatigue and regular Hypos.
It impacts it so much. Both my endo and therapist suggested that I stop working to concentrate on my health. I am currently searching for disability, and should be having a hearing soon to determine if I can get assistance.
Chronic pain, fatigue, and nausea make working difficult.
Does have an impact due to brain fog and fatigue mainly
Fatigue, brain fog, mobility
Difficult to work due to exhaustion and brain fog, and pain
Significant impact prior to metreleptin. I could not work full time due to poor health and energy. With treatment I am able to work full time.
I struggle to lift things. I can't stand for a length of time. Sometimes find it hard to concentrate. Fatigue at work.
It makes it much harder to concentrate due to muscle pain and fatigue. Plus it is extremely difficult to juggle working full time, family life plus other commitments due to exhaustion
None , just have to get on with it
I am retired due to ill health/not fit for work. I was retired on ill health grounds age 53
Fortunately retired as left work age 53 on health grounds
Chronic Fatigue, tiredness and brain fog were the main aspects that restricted my academic performance since my energy level is drastically low, hence carrying out assignments was a major challenge. It is difficult to ardent classes then have the energy to study independently after at home; followed by assignments. It felt exhausting and drained me mentally and physically. Additionally, sitting for long periods of time was very difficult for me as my muscles and joints get sore. I also used to zone out in classes as my brain felt overwhelmed and so unable to process information.
Cannot work due to extreme pain and tiredness
I'm of sick at the minute
Doesn't apply
High impact. It is hard to concentrate with brain fog, I am forgetful and I often struggle to stay awake because of the fatigue. In addition, I often run out of energy and have to take breaks

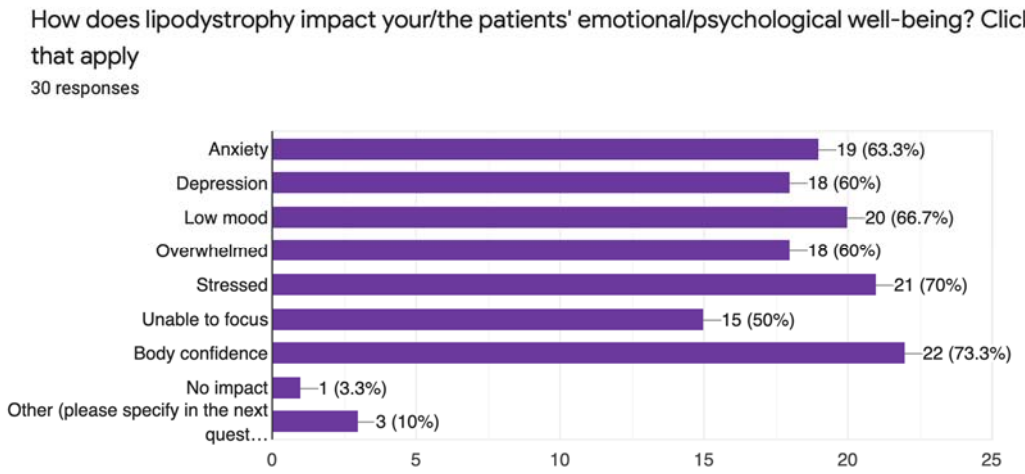


Please describe 'other' in relation to your/the patients' work/study situation (if applicable)

Not able to attend school regularly
Full time
Find it hard to work as want to sleep all the time
I am a full-time teacher, considering leaving the profession due to chronic health issues related to lipodystrophy
I was a full time er nurse for 10 years, now am staying home with my toddler full time

Is your/the patients' performance at work/school affected by your/their lipodystrophy? If so, please explain

I get so tired that it is hard to keep awake when I'm working. The brain fog can affect my capability to perform at my full potential and can leave me prone to missing things and making mistakes - which previously would have been very out of character for me
No
Not able to focus on studies
Yes - pain from cramps and spasms
No try to make the best of a situation
Does not effect my ability to work
Yes
I cannot work more than 5 hours straight due to extreme fatigue, Hypos, ability to focus
Yes. I don't feel that I can preform my best as a teacher. On high pain days i cannot move around the room to support students, and chronic fatigue makes prepping difficult and occasionally makes me irritable
Some days due to sever nausea/fatigue/body aches I'm unable to go to work as I can't manage to get out of bed - so the above do debilitate me.
Yes due to brain fog and fatigue
Yes, it was always a struggle
I had a difficult time learning through school as I was so hungry.
Yes, I sometimes find it hard to concentrate. Feel tired all the time. Standing for periods of time causes pain. Walking around is painful.
No, but only because I rest a lot when I am not working as I don't want my work to be affected. Having to rest when not working impacts my family life instead
No, do not work, retired
Yes, as explained above, my academic performance was drastically affected by my medical condition. This is because I get overly fatigued and so my ability to carry out study-related tasks was hindered. I also struggled to focus for extended periods of time meaning that I zoned out in classes.
Always tired to weak to do jobs painful when doin jobs
As above - It is hard to concentrate with brain fog, I am forgetful and I often struggle to stay awake because of the fatigue. In addition, I often run out of energy and have to take breaks



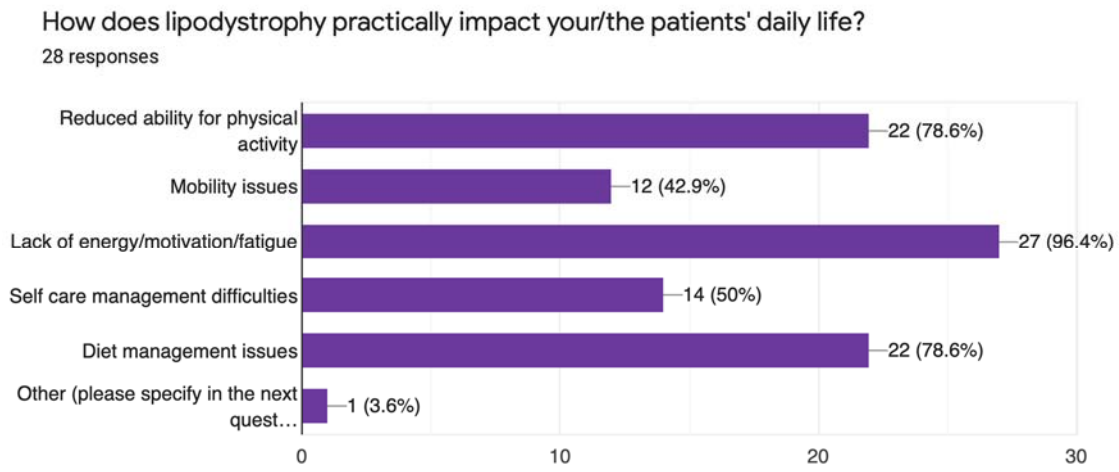
Please specify 'other' in relation to your/the patients' emotional/psychological well-being (if applicable)

I suffer with anxiety and depression, and I hate my body image.i struggle to concentrate and my memory is terrible.
It wouldn't let me tick more than one so I would like to add: depression, low mood, overwhelmed, stress, low body confidence and unable to focus.
All of the above. Multiple selection not working
Every once in a while I feel depressed or anxious about lipodystrophy, but overall I have been in a positive mental/emotional state and have not struggled with any severe issues.
Not able to participate in societal gatherings
Not knowing what future may hold.
Extreamly bad tempered
Body issues and unstable personality disorder
I also suffer from ADHD and PTSD
Feels sad

Describe the emotional/psychological impact of this disease on your/the patients' daily life

Some days I feel like this disease sucks the life out of me and I can feel so low and worthless. At very bad times I can feel like I'd be better off not here. When these feelings happen, I have to bottle this all up inside and try to carry on with my daily routine. It can take just about everything out of me going to work and putting on a charade that when I get home I can't eat or socialise. I just have to go to bed.
Feelings of little self worth worsen fatigue and it gets into a horrible cycle of fatigue and feeling terrible about it's impact. Frequent bouts of worsened depression and anxiety leads to social withdrawal
Low self confidence and feeling of rejection
A diagnosis gave me an explanation of my body shape which has a huge emotional impact on self image and esteem. My torso always fat yet my limbs were muscular. I believe that I look like a male with breasts.
You just never know what will happen and when so you are always on your guard mentally and physically
Can feel emotionally drained when particularly having a bad day you end up feeling angry So may feel the need to snap at everyone but that just makes it worse
Try not to let it bother me
Low self esteem because of body shape and appearance

quality of life hugely impacted by fatigue and lack of stamina
Every day is different
It is a constant struggle. I have been in therapy for over 30 years. I have attempted many suicide attempts, have been placed in psychiatric hospitals, and even went to a theraputic school for my senior year of high school. I am still currently under a therapist for my psychological issues.
My psychological symptoms are extreme and exasperated by lipodystrophy. I was recently hospitalized for anxiety/depression and binge eating disorder. I am constantly hungry and anxious about my health and about how others view my body and eating habits
As I have got older my body shape has changed and I'm very self conscious of this and also when my tummy bloats out its very unsightly and I like to just stay at home, but working full time this is difficult, so it does depress me. The fatigue also hinders work and family life, all the joint aches and pains.
Struggle to feel like a good mom and wife because I have no energy, little libido, and always hurting
I am constantly concerned about how others view me physically and the judgements that are made. I feel unable to date due to my body confidence
I worry every day about the "what ifs" for myself and my family. This often makes my mood low
Always think people are better than you , your ugly and are going to die soon anyway
It has totally taken over my life as I constantly worry about what complication of lipodystrophy I am going to suffer from next and I worry about the potential progression of the ischaemic heart disease, which would lead to my early death. Local hospital has indicated that further interventions such as stents etc would not be offered due to the complications I suffered during heart surgery 3 years ago
Constant worry and anxiety issues, difficulty eating out, prefers to be home anyway. Lack of confidence and needs constant reassurance. Does not like to drive and will only go out if I am there too.
As Lipodystrophy is a very life limiting condition, it is a constant battle to stay strong, it has affected every single aspect of my life to socialising, career, education, forming relationships, self-care, carrying out day-to-day tasks, household chores. Ot is therefore not easy to stay sane at times when all your life opportunities are taken away or are limited. Along with physical barriers I faced extreme bullying due to the way I look (too thin), this shattered my confidence drastically as it is not my choice to decide how I look, Its God given. Moreover, the lack of emotional and physical help from family is an area of my life that is upsetting and unjustified. I have realised now that I am not dependant on anyone and it is ok to not have family though family should be there for each other but I guess I didn't have it so that I could be stronger. It is also frustrating to know that there is a treatment out there (Metreleptin) but yet I cannot gain it as it is not granted to FPLD, upon speaking to experts from UK, USA Turkey and Spain, I was told that I should be on this treatment as I qualify for it but because I'm in the UK; I cannot have it, it implies that money matters and people don't since Lipodystrophy is rare so why give such an expensive drug to a minority group of population it seems. I get episodes of low mood and depression but that is normal for my situation and it is something I have accepted and learnt to live with.
Emotionally tiring, always feel like a burden
Doesn’t like to take pictures, always worry what others think, or might say
I struggle with my mental health. This diagnosis has been a little like grieving - grieving for the person I should/could have been. I find it difficult to open up to people and because of my body image issues, I have never been in an intimate relationship, despite approaching 40 years old. It can be hard to stay positive when it feels like all the life has been sucked out of you. I am constantly in pain and anxious about what the future holds.



Please specify 'other' in relation to the practical impact of lipodystrophy on your/the patients' daily life (if applicable)

Everyday is challege. Some days are good while some are too bad.
Having to shave face 12 hourly
Heart palpitations
It makes it difficult if I want to eat out as many cafes/restaurants will not cater for my diet. Some cafes/restaurants have said they can cater for my diet and then just produce food which I am unable to eat. I eat little and often and this is not always possible to do when away from the home.
Has no strength or energy

Describe the physical impact of this disease on your/the patients' daily life

I struggle daily with all my health conditions and I still have to work full time, so on my days off I have no life as I'm lethargic and In pain. I tend to suffer as this condition is rare and people don't understand how I'm feeling, which then gets me depressed as no one understands how much I'm actually suffering.
I experience too much pain if I over do it with physical activities. This can make it difficult with loved ones. For example, my partner sometimes forgets and thinks I'm just being lazy when I need to take a break from painting when he can easily just carry on. But the pain can build up making it difficult to carry on. The fatigue causes extreme lack of motivation which can make it difficult for me to manage my medication or my diet
Wake up with tight, painful muscles, mostly in my legs, especially in colder weather. Difficulty walking and non driver so I rely on lifts or public transport.
Low energy levels and therefore lesser outings and indoors also reduced energy levels
Needing to sleep more oftern
The fatigue can wipe you out completely so you have no energy to try and exercise or even getting to and from work is hard work. You leave early so that you can get a seat on the bus or tube as you need to sit down.
Aching limbs. Sometimes cramp in calf during the night
Need to rest / nap most days and unable to do more than one or two chores in a day
Some days, I can't even get out of bed. It effects my relationships with my friends and family. I dont have the energy to do things with my friends and family and miss out on activitites that I can not do.
Chronic pain and fatigue limit what I can do as far as daily functioning
I'm unable to do the things I used to, I walk my dog for about 1 hour twice a day and then that's it, I am in a lot of

pain after I change beds, (my husband has to do this now), unable to bend for long periods of time, i.e. Gardening as this causes dizzyness
Constantly thinking about food, always feeling guilty for not having enough energy
I have very little endurance due to fatigue. Any high impact activity is impossible due to joint pain.
I am so physically exhausted from work, other aspects of life have to wait or be cancelled
Angina stops you doing cardio exercise
I have had to give up my hobbies such as reenactment and competitive archery and archery judging as I am unable to continue with these due to the extreme tiredness, and angina
Does not do anything like what she used to do, due the above issues.
Please read above for a detailed description, but in short I suffer from several conditions due to FPLD such as Cardiac, respiratory, chronic fatigue, kidney disease and more. These affect my daily life as I struggle to carry out basic tasks such as household chores, work or even go out to socialise since it is drastically exhausting. Additionally, I cannot drive the it is an added obstacle to get from one location to another.
Always feeling Tired
I get so tired that often by the time I get home from work I am good for nothing, I have no energy even to cook properly and so my diet can be impacted badly. Instead of making use of my evenings and weekends for practical chores, or even enjoyable activities or socialising, I often find I have no energy and have to rest. This is very frustrating, adds to the feeling of being lonely and overwhelmed and means I fall behind on important things

What impact did/does lipodystrophy have on your/the patients' relationships and social activities?

I rarely do anything apart from work and rest.
A great deal, not many can fully understand as a lot of the symptoms aren't visible on the outside. So the fatigue for example can't be seen by others. This can lead to a misunderstanding with friends or family and prevent you from partaking In every social activity
The impact on my first marriage was devastating. My ex husband accused me of using it as an excuse to "be lazy" The randomness of some days of fatigue or high pain levels means plans have been frequently cancelled and friendships have been damaged by this. The psychological impact has taken it's toll alot since moving towns last summer. I have not had the confidence to go out and make friends. I am usually quite extroverted in nature but this has changed as big physical health knocks have all but killed my self esteem.
Social life is almost absent
Exhaustion and pain affects ability to perform daily tasks and limits social interactions when too affected.
You make excuses not to go out with friends if you know it's going to exhaust you!
I get extremely tired, even if i've had a nap during day can make an evening out very short when I can't stay awake, that can be upsetting and disappointing when you want to socialise for longer
None
No close relationships apart from family
Often cannot participate in activities or go out due to lack of energy so not having a fulfilled life - this can create tension with partner and other family members and friends
N/A
I miss out of many social events due to pain fatigue and nausea
I don't like to go out and socialise, I prefer to stay home.
Hard to be a wife and mother when I can barely care for myself; financially impacts too
Fatigue keeps me from regular social activity. Anxiety also inhibits social activity
I often cancel or avoid plans because of exhaustion, low mood or anxiety
You don't have a relationship, who wants a freak , who has no future, will die early
Unable to go out without someone with me
Lost touch with a lot of friends due to social isolation as a result of the strict diet, tiredness and issues above. She has given up all her activities she loved doing; Re-enactment, Archery as a competitor and Archery Judging.

It is a life changing experience for anyone in a relationship with someone that has a severe illness, since they are required to adapt and accept the other person's limitations. This can be very difficult and at times cause arguments such as on sharing workload, physical adjustments, mood fluctuation and more. It is therefore a continuous process of compromise and adjustment as the condition progresses. Moreover, due to my extremely thin appearance, it has always been tricky in finding a partner that looks past the physical appearance and focuses on the inside as that is what should matter. Our body is simply a shell that fades away but our soul is immortal. Even when you do find someone who loves you for the person you are it may still spark conflicts and adjustment issues like with any relationship but it is far more with a condition.
I can't attend many social activities
Likes to stay home a lot
I find it difficult to open up to people and because of my body image issues, I have never been in an intimate relationship, despite approaching 40 years old. Family struggle to understand how I feel (physically and emotionally) which can sometimes put a strain on those relationships. I find it very difficult to make friends and my social circle is practically non-existent

What impact has lipodystrophy had on your immediate family unit?

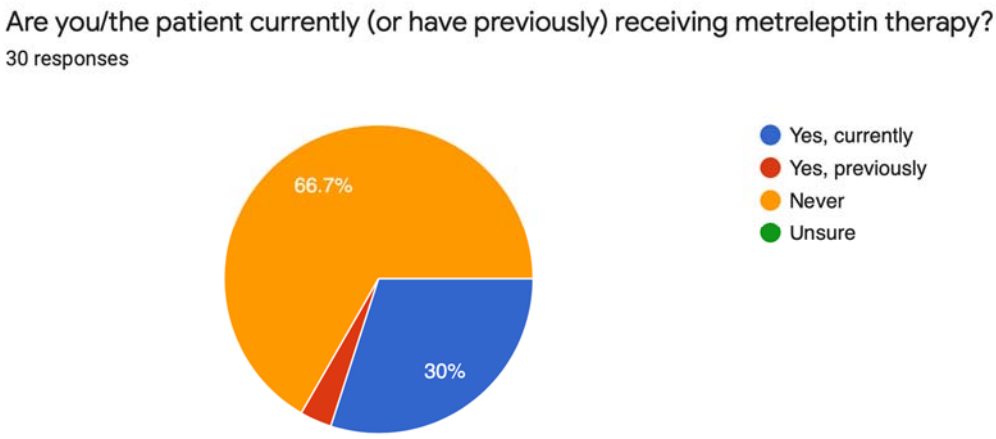
I'm very snappy with my family members as I'm constantly tired and have no energy.
Anxiety and fear that something will go wrong with my health again and that i'll be hospitalised
I cannot play with my daughter (7yo) as much and as often as I want. I feel like she misses out on a lot. My husband gets frustrated at times as the lions share of housework falls to him. Both he and my daughter worry alot when I become unwell and this is very distressing for them.
Maybe some "survivor's guilt" or guilt about passing on this disorder
Strangely we are bound together
My daughter has Lipodystrophy more severely affected than myself, I feel guilty about this, however we try to support eachother.
My family are very supportive but you do have to remind them that you can't do things which are normal to them but are hard work for you!
None family are understanding
None
They all walk on egg shells around me
Cannot do as much with them as i'd like and don't feel i can support/help them as much as i'd like
Both sons have Lipodystrophy
It broke my family apart for awhile. I had to be sent to a therapeutic school because I was so out of control. It causes issues in my marriage because I never feel well. Its hard for others to understand. They say just get up and do it. Easier said than done.
I feel as though I cannot uphold my share of the household responsibilities which puts a strain on many relationships
I feel very guilty that I am unable to do the things I used to and my husband has to do most normal routine household jobs.
Same as above
My family is very aware that I am high risk during Covid19. They are also concerned about my general well being long term.
They find it hard to notice when I'm struggling because I don't look ill.
My relationship has suffered because of my constant low mood, anxiety & poor body confidence
They don't always understand
Restricted my partners activities as he constantly worries about how I am and is unwilling to be away from me
Constant worry, do not like to leave on her own and have become more of a carer. This has also reduced the amount of time I spend doing outdoor activities,
My family has always been too busy with their own life, this includes parents and siblings, hence I have had to deal with everything alone. My condition therefore did not impact my family since I moved out at an early age to get a better life as there was no family support anyways. I am from a broken family thus we all had to manage our lives alone basically.

They need to help me alot so they don't have alot of free time to do the things they want to do
We never talk about it
I live alone

What are the top three things that you/(and/or)the patient struggle most with regarding your/the patients' lipodystrophy?

My pain, my excessive hair and my body aches.
Fatigue Pain Fear of how fast the disease is progressing
Fatigue, pain, psychological distress
Guilt Receiving stares/questions
No physician in our city is aware of this disease and treatment so find it difficult to get treatment for common ailments even. We are aware of effective Metreleptin treatment but cannot give it to daughter due to its unavailability Anxious about her wellbeing in future
Tiredness, hunger, looking manly
Pain, digestive issues vomiting liver pain, exhaustion
The constant diet that doesn't seem to show the effects- your legs and arms get smaller but the stomach fat and face fat never want to go away. The constant fatigue which seems to get worse every few months which seems to link with the leg pain The cramps, restless leg and spasms that stop you from sleeping well
Bloating and flatulence can be quite painful and the aching legs that just don't seem to ease up
Body image , having to take large amounts of insulin
Pain, looking pregnant and having no fat on my bottom to sit down.
Body image Fatigue Diet and exercise
Fatigue physical appearance limitations in what i can do / achieve
Tiredness, headaches, ability to focus
Pain, not knowing how my body is going to react for that day, and my own mental stability.
Pain, fatigue, diabetes/blood glucose management
Nausea/Brain Fog/Fatigue
Fatigue, brain fog, mobility
Constantly obsessed with food, something always hurts, always exhausted
Fatigue, food focus (much improved with metreleptin) body image
Diet. Physical exercise and mood.
Pain. Fatigue. Low self esteem
Diet, Energy and complications of FPLD2 as i wonder of the medical profession had listened to me sooner whether I would not have all the complications I have now as I would have been seen and diagnosed earlier as well as given all the relevant information earlier to manage the FPLD2
1. Losing the leptin medicine as this has been the only thing that has given my wife hope and it works! 2. Eating, due to the very restrictive diet and a large proportion of eating establishments not being able to cater for it. 3. Losing so much time we used to spend outside doing things.
The first one is Chronic Fatigue as I have limited energy thus need to prioritise, for example I can either go out (including grocery) or carry out household chores (that too in stages split over a few days). I feel both mentally and physically exhausted without even doing much and so have to nap a lot throughout the day.

The second one is cardiac condition due to which I get very breathless upon limited physical exertion and I am required to excessive to keep my sugar level low but I can't do this as I get short of breath. So everything is linked together. I get short of breath even by walking short distances which is very worrying and so I have to think carefully about using the very little energy I have. Third is my stomach issues which cause diarrhoea, nausea and increased hunger. These are all linked as uf I have nausea I cannot eat but then I have increased hunger and if I eat i get diarrhoea. I get these every day and I need the mensroom several times a day as my body cannot retain food. I get severe hunger pains sometimes minutes after i've had a meal hence I have to stock up on food which is very costly as I can eat way too much some days, additionally, I need healthy meal prepared at the same time.
Mental health Managing medication Body image
Pain tiredness fatigue
Feels like I'm alone, Nobody really understands me, Feels depressed
Fatigue/energy Body image Mental health (before taking leptin, hunger was number 1)



If yes, for how long have you/the patient been receiving metreleptin treatment?

I received it briefly in late [redacted], stopped due to pregnancy. I restarted in [redacted] (??) And continued treatment until February [redacted]. Again, stopping due to pregnancy.
10 years
Not received metreleptin but would very much like to receive it
5 years
Many years about 10 maybe a little longer I am unsure

Approx 2 years
Not available to me
No one will give it to me
5 years
2.5 years
2.5 years
7+ years
12 ½ years

What benefits have you/the patient experienced from treatment? Explain as many as possible

Feeling satisfied by food for the first time in my life.
Triglycerides back to normal, appetite back to normal, no more fatty liver
Appetite suppression, stable blood fats, delayed liver deterioration
The hunger issues I had to begin with have improved a lot I used to be very hungry all the time even though I had eaten I would immediately feel hungry again now I don't get that feeling as strongly anymore I can now get on without eating more than I need to. My fatty liver has gone down considerably as when it was first enlarged it was very uncomfortable It helps keep my weight under control. When I've been off the Leptin for a short period of time I have put weight on and when I have returned to normal use I find my weight is manageable I feel in general it helps different aspects of my mental and physical health. If I wasn't on it I think I would have been in hospital more times with pancreatitis, since being on Leptin I have not had one episode.
Life changing! It allows me more freedom as I no longer have to invest huge amounts of Insulin daily. It has kept my weight down so no yo-yoing. It has been very liberating as most of my Lipo health issues have been easily control.
Significant improvements in hyperphagia, significant improvement in immune system, significant improvement in fatty liver, improvement in trigl6and A1C
Extreme hunger has lessened Diabetes is under control so I no longer require conventional diabetes medication
Diabetic control is now perfect and requires no diabetic medicine or input. Mixed hyperlipidaemia again now within normal limits form being extremely and dangerously high despite medicine and restricted diet. Preventing further fat build up in her coronary arteries, which she could not tolerate. The fat build up in the chin area has now gone. The constant hunger issue has resolved.
I don't feel hungry all the time Fatty liver has improved A lot less pancreatitis Diabetes easier to control
Incredible. My hunger disappeared almost over night. The fat in my liver reduced by over 75%. My insulin requirements were cut in half

What are your/(and/or) the patients' concerns if metreleptin treatment is withdrawn?

Those who respond positively to the treatment will have their one defence against the relentless nature of the disease stripped away. I said it in the [redacted] meeting and I will say it again here; to a healthy person it is hard to understand, but the impact of hunger cannot be overstated. Financially, physically, mentally. Feeling full shouldn't have to feel like a revelation to anyone, especially not to those whose treatment is so heavily dependent on good diet. NICE want data on the hunger impact of Metreleptin and I say it's already there. Hunger is a roadblock to achieving the quantifiable results of hba1c, lipid profiles etc. Metreleptin is the only wrecking ball we have to get rid of that obstacle.
Withdrawal of Metreleptin treatment would be a tragedy for many patients who need it. Metreleptin is a lifesaving treatment for many - without leptin, my triglycerides would be through the roof and numerous organs would be full of fat, putting myself at extreme risk. And I am one of the lucky ones. There are other patients who, before Metreleptin treatment, were near death. Metreleptin has saved many lives, and it is critical that patients have access to this lifesaving treatment.
Metreleptin should be easily available to all patients in a globe as that is the only treatment available currently
It would be devastating and my general health would deteriorate, I would be very frightened about my future without Leptin, I believe it has delayed crisis outcomes.
I feel I would have more premature health complications and a less likelihood of surviving these complications if I was not on Leptin
That I will revert to being severely resistant to Insulin with all the issues that entails. It will have huge consequences on my physical and mental health as I depend on Leptin to keep me on a positive level and excellent diabetic control.
I am terrified of loosing access and going back to constant hunger and being sick 3 out of ever 4 weeks. I will not be able to maintain my employment.
The FPLD 2 and complications would resurface Medication would be required for my diabetes

The ischemic heart disease would progress further, particularly as the combination of ezetimbe, atorvastatin, bezafibrate and restricted diet was not enough to keep my diabetes and mixed hyperlidaemia under control which in turn would result in my ischemic heart disease progressing further and an early death
Absolutely terrified, as the heart disease will worsen, as will the diabetes, hunger, mixed hyperlipidaemia. This worry is constantly on our minds
My life will be become majorly harder than it already is. My life will be shortened. My mental health will further deteriorate
I'm terrified of going back to a life without leptin. The hunger is all consuming and incredibly painful

Is there anything else you would like to share?

I just hope we can finally get some answers to why my body is making me feel like a 80year old but it's image is muscles and manly body and hairy when I just want to be a lady
We request you to kindly consider our request to provide us Metreleptin treatment. Please
With a disease I was unaware of until I was diagnosed in [redacted] as a [redacted] year old it is very daunting. The Leptin offered to me I feel is giving me the best possible outcomes of this disease as there are so many ailments that come with it and at different degrees of 'harm' to the body. If I wasn't having the Leptin there trying to maintain a balance in my health I think I would be more unwell than I have been.
Leptin has been the ONLY drug that has enabled me to control my severe insurance resistance and have a normal life.
I hope that the medical field starts to recognise how hard lipo is to live with, and that if there is a medication that might help people with our condition, it should be available to the people who need it, at a reasonable price.
This is a disease that I had never heard of till now, it is quite scary actually when I look into my family history and all my problems run in my Granddads family on my Mums side, I have an aunt who I believe also has this disease but has never spoken to anyone about it - only I told her about it, she is severely ill with all the complications that run along with this disease and her own GP does not want to discuss it with her as they know nothing about it as it is that rare, I think a lot more should be taught about this. For the last 10 years I have had so many tests for heart problems after my heart attack and heart bypass and nothing was ever picked up. It was only when I went to see a private cardiologist who said to me that he couldn't believe that I was a type 2 diabetic as my body shape and weight and BMI of 22 do not correlate, he said to me there is an underlying issue here and he then put me in touch with [redacted] and specialist in the field, I had DNA bloods taken and it was confirmed that I have Familial Partial Lipodystrophy, if it wasn't for the private cardiologist I could have probably gone another 10 years still having heart problems. I had a quadruple heart bypass in [redacted].
Metreleptin changed my life. I cannot imagine how I managed 37 years in the world I was living. No human should have that hunger. My body functions so much better with treat. I fear I will die without it.
The metreleptin therapy is extremely important to me as it has allowed me to lead a somewhat normal life and the withdrawal of this treatment will be devastating to not only me but also my family as the withdrawal will mean that my health will start to deteriorate and they will have to watch knowing that there is nothing that they can do to help. Myself and my family are unable to afford to fund the metreleptin privately
The metreleptin was an absolute lifeline and the difference it has made to us is incredible and to think about losing it is devastating to us. We would not be able to fund it privately and so puts us in an unimaginable position and one we do not want to happen.
I would at least like to have a chance to get on Metreleptin even if it is for a short period of time just so I can see what difference it would make to my quality of life. It may even help to cure or limit some of my major symptoms thus I'd like to try it. I would also like to express that I was diagnosed at age 25 despite my clear symptoms but no doctors believed in such a condition and blamed my thin appearance to Anorexia. I don't understand how it took 25 years just to get a genetic test conducted, as my diabetes and other issues could not be self-inflicted this there must be some underlying condition causing my symptoms, yet no medical professionals took it seriously. Even today, I receive very little medical help or guidance and examination as no one sees the seriousness of this condition. I have been advised to have regular checks at least every three months for my heart but I do not get these. My Endocrinologist is the only doctor who believed my symptoms and diagnosed me because of which I am on vital medication and he keeps a close check on me, which I am very grateful for.
I always hope there would be more information out there, Especially to Doctors so they are more educated on this.

03.04.2020

Highly Specialised Technologies Evaluation: **Metreleptin for treating lipodystrophy [ID861]**

Prepared by [redacted], [redacted] and [redacted], Wolfson Diabetes and Endocrinology Department and Institute of Metabolic Science, Addenbrooke's Hospital, Hills Road, Cambridge, CB20QQ

Thank you for your letter of 5th March 2020 inviting the National Severe Insulin Resistance (NSIR) Service at Addenbrookes Hospital to submit evidence prior to the HST evaluation of metreleptin for treating lipodystrophy due to be held on Thursday 8th October 2020**.**

The NSIR Service is a highly specialised NHS service based at Addenbrooke's Hospital in Cambridge. The service is funded directly by NHS England. The NSIR service sees both adults and children with rare syndromes of severe insulin resistance. The lipodystrophies are a group of disorders where severe insulin resistance is a key feature. 70% of patients seen by the service have a diagnosis of lipodystrophy.

The NSIR service was established with three basic aims:

1. To provide accurate diagnoses for patients and their carers given the rarity of the disorders
2. To improve key clinical outcomes e.g HbA1c, circulating triglyceride levels and liver fat content, with a view to reducing long term complications
3. To educate other centres around the UK about these rare disorders

The service is built upon our collective experience in this disease area which stretches back to 1991 in the case of [redacted].

We are currently the only centre in the UK permitted to prescribe metreleptin therapy for patients with lipodystrophy as part of an expanded access programme. We currently care for approximately 20 patients with lipodystrophy who take metreleptin therapy. It is important to appreciate that we were not the first centre to initiate trials of leptin use in patients with lipodystrophy and we have never undertaken this activity as part of a research study. This was largely done as we were supporting rather than competing with the NIH initiated work in the USA. **Our patients participating in the expanded access programme were provided with leptin on a "compassionate use" basis so were not enrolled according to specific entry criteria, and in many cases they would not meet the currently proposed criteria for metreleptin therapy. This is very important to keep in mind when reviewing the expanded access programme data.**

Before addressing the points you raise, we would like to make a few general introductory remarks as our reading of the documents you provided suggests that some basic points are imperfectly understood.

- Lipodystrophies are all defined by a primary deficiency and usually also dysfunction of adipose (fat) tissue
- The primary physiological function of adipose tissue is to store excess energy (calories). This activity is severely disrupted in lipodystrophy and results in the need to store excess calories (as triglyceride) in the liver, muscle, pancreas and other sites, which are not designed for this purpose. This is known as ectopic fat accumulation.
- **Ectopic fat accumulation underpins almost all the subsequent metabolic problems associated with lipodystrophy** including non-alcoholic fatty liver disease

(NAFLD) (which can progress to steatohepatitis, cirrhosis and cancer), hypertriglyceridemia (which may lead to pancreatitis), severe insulin resistance and treatment resistant Type 2 diabetes with its attendant complications, and polycystic ovary syndrome in women.

- The metabolic problems listed above typically start relatively early in life and are refractory to conventional therapies.
- The focus of treatment is to alleviate the imbalance between energy intake and place to store the energy safely. Clearly one could try fat transplantation and this does help in mice but is not yet feasible in people. The other option is to limit calorie intake. This however is extremely challenging as the absolute or relative leptin deficiency experienced by lipodystrophic patients renders most of them very hungry all the time.
- As a reference point for the importance of leptin in regulating appetite, congenital leptin deficiency in mice and humans leads to morbid obesity from infancy in every single affected mouse or human.
- Patients with generalised lipodystrophy essentially have undetectable leptin levels so tend to eat as much as people with congenital leptin deficiency. It is worth remembering that funding approval already exists in the UK for metreleptin treatment for children with congenital leptin deficiency.
- It is likely that metreleptin has some additional metabolic benefits, particularly to improve the body's sensitivity to insulin above and beyond its affect to suppress appetite (see below Brown et al).
- Leptin replacement in people with generalised lipodystrophy is highly effective in reducing ectopic fat accumulation and thus diabetic control, NAFLD and hypertriglyceridemia – nothing else works, so a placebo controlled trial will never be done and would be unethical in our view.
- In patients with partial lipodystrophy, metreleptin therapy has also been very helpful as an adjunct to conventional therapies in some cases.
- Lipodystrophy syndromes have a very high morbidity and premature mortality. Eight patients with lipodystrophy attending our service have died since the service started. Three with generalised lipodystrophy (median age 26.7 years, range 20.7 to 49.6 years) and five with partial lipodystrophy (median age 57.9 years, range 52.8 to 61.7 years).

Many patients with lipodystrophy are distressed by the cosmetic effects of lack of fat, which can be severe. Unfortunately metreleptin therapy has no impact on the underlying cause of the lipodystrophy and will not restore fat where it is absent. So in short, metreleptin therapy helps to reverse the imbalance between excess energy intake and storage capacity in fat tissue, and as such is critical to the management of metabolic disease in patients with generalised lipodystrophy in particular where there is no other effective therapy. It is also very helpful in some patients with partial lipodystrophy and severe refractory metabolic disease.

As a stakeholder we have addressed the points suggested in your letter.

1. The relative effect of metreleptin on disease progression and important outcomes for patients such as hyperphagia

The clinical trials of metreleptin did not have a placebo group as it is difficult to incorporate placebo groups into trial design in very rare diseases due to the very small numbers of eligible patients. The regulatory authorities have deemed that there is enough evidence of efficacy that product licences have been granted for metreleptin therapy in Japan, USA and Europe. We would suggest that each patient could be seen as acting as their 'own control' if their metabolic status at baseline is compared to their metabolic status on-treatment. The

metabolic improvements seen with metreleptin, which have been demonstrated in several clinical trials, are highly unlikely to be explainable by solely a 'placebo effect'. In our clinical experience some patients treated with metreleptin can stop insulin therapy completely or significantly reduce their insulin dose, and may also have a normalisation of triglycerides, reduction in liver size, improvement in liver function tests and fewer pancreatitis episodes. Whether the mechanism of action is solely due to reduction in hyperphagia is unclear. There is good evidence that metreleptin reduces hunger/appetite in patients with lipodystrophy and also that metreleptin still has a benefit when food intake is controlled.

***Leptin Substitution in Patients With Lipodystrophy: Neural Correlates for Long-term Success in the Normalization of Eating Behavior**. Schlögl H[1], Müller K[2], Horstmann A[3], Miehle K[4], Püschel J[5], Villringer A[6], Pleger B[7], Stumvoll M[4], Fasshauer M[5]. Diabetes. 2016 Aug;65(8):2179-86. doi: 10.2337/db15-1550. Epub 2016 May 10*

In this study, resting state functional MRI scans and extensive behavioral testing assessing changes in hunger/satiety regulation were performed during the first 52 weeks of metreleptin treatment in nine patients with LD. Resting state connectivity significantly increased over the course of metreleptin treatment in three brain areas. Behavioral tests demonstrated that perceived hunger, importance of eating, eating frequencies, and liking ratings of food pictures significantly decreased during metreleptin therapy. Taken together, leptin substitution was accompanied by long-term changes of hedonic and homeostatic central nervous networks regulating eating behavior as well as decreased hunger feelings and diminished incentive value of food.

***Beneficial effects of leptin substitution on impaired eating behavior in lipodystrophy are sustained beyond 150 weeks of treatment.**. Püschel J[1], Miehle K[2], Müller K[3], Villringer A[4], Stumvoll M[2], Fasshauer M[5], Schlögl H[6]. Cytokine. 2019 Jan;113:400-404. doi: 10.1016/j.cyto.2018.10.012. Epub 2018 Oct 24*

A prospective study with measurements at baseline and at >150 weeks of metreleptin treatment was performed. Five female lipodystrophy patients with indication for metreleptin were included. Behavioral aspects of hunger- and satiety regulation were assessed by validated eating behavior questionnaires and visual analog scales assessing hunger and satiety feelings before and after a standardized meal. Hunger rated on visual analog scales at 120 min after the meal significantly decreased from 46 ± 10 mm at baseline to 17 ± 6 mm at long-term assessment. Furthermore, satiety at 5 and 120 min after the meal significantly increased from baseline to long-term assessment (5 min: 70 ± 7 mm to 87 ± 3 mm; 120 min: 43 ± 10 mm to 79 ± 8 mm). On the Three Factor Eating Questionnaire, the mean value of factor 3 (hunger) significantly decreased from 9.2 ± 0.2 at baseline to 2.6 ± 1.5 at long-term assessment. In the Inventory of Eating Behavior and Weight Problems Questionnaire, mean values for scale 2 (strength and triggering of desire to eat) and scale 7 (cognitive restraint of eating) significantly decreased from baseline (31.6 ± 4.8 and 11.4 ± 2.2, respectively) to long-term assessment (14.0 ± 2.1 and 10.0 ± 1.9). This study presents evidence that that long-term metreleptin treatment of >150 weeks has sustained effects on eating behavior with increased satiety, as well as reduced hunger and hunger-related measures.

***Metreleptin-mediated improvements in insulin sensitivity are independent of food intake in humans with lipodystrophy.** Brown RJ[1], Valencia A[1], Startzell M[1], Cochran E[1], Walter PJ[2], Garraffo HM[2], Cai H[2], Gharib AM[3], Ouwerkerk R[3], Courville AB[4], Bernstein S[4], Brychta RJ[1], Chen KY[1], Walter M[5], Auh S[6], Gorden P[1]. J Clin Invest. 2018 Aug 1;128(8):3504-3516. doi: 10.1172/JCI95476. Epub 2018 Jul 16*

Patients with lipodystrophy were hospitalized for 19 days, with food intake held constant by a controlled diet. In a non-randomized, crossover design, patients previously treated with metreleptin (n = 8) were continued on metreleptin for 5 days and then taken off metreleptin for the next 14 days (withdrawal cohort). This order was reversed in metreleptin-naive patients (n = 14), who were reevaluated after 6 months of metreleptin treatment on an ad libitum diet (initiation cohort). With food intake constant, peripheral insulin sensitivity decreased by 41% after stopping metreleptin for 14 days (withdrawal cohort) and increased by 32% after treatment with metreleptin for 14 days (initiation

cohort). In the initiation cohort only, metreleptin decreased fasting glucose by 11% and triglycerides by 41% and increased hepatic insulin sensitivity. Liver fat decreased from 21.8% to 18.7%. In the initiation cohort, changes in lipolysis were not independent of food intake, but after 6 months of metreleptin treatment on an ad libitum diet, lipolysis decreased by 30% to 35%. This study suggests that metreleptin improves insulin sensitivity and decreases hepatic and circulating triglycerides and that these improvements are independent of its effects on food intake.

Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. *Brown RJ[1], Oral EA[2], Cochran E[3], Araújo-Vilar D[4], Savage DB[5], Long A[6], Fine G[6], Salinardi T[6], Gorden P[3]. Endocrine. 2018 Jun;60(3):479-489. doi: 10.1007/s12020-018-1589-1. Epub 2018 Apr 12.*

Patients (n = 66) aged ≥6 months had lipodystrophy, low circulating leptin, and ≥1 metabolic abnormality (diabetes mellitus, insulin resistance, or hypertriglyceridemia). Metreleptin dose (once or twice daily) was titrated to a mean dose of 0.10 mg/kg/day with a maximum of 0.24 mg/kg/day. Significant mean reductions from baseline were seen at month 12 for HbA1c (-2.2%, n = 59) and FPG (-3.0 mmol/L, n = 59) and mean percent change in fasting TGs (-32.1%, n = 57) (all p ≤ 0.001). Reductions from baseline over time in these parameters were also significant at month 36 (all p < 0.001, n = 14). At month 4, 34.8% of patients had a ≥1% reduction in HbA1c and 62.5% had a ≥30% reduction in fasting TGs; at month 12, 80% of patients had a ≥1% decrease in HbA1c or ≥30% decrease in TGs, and 66% had a decrease of ≥2% in HbA1c or ≥40% decrease in TGs. Of those on medications, 41%, 22%, and 24% discontinued insulin, oral antidiabetic medications, or lipid-lowering medications, respectively. Mean decrease in liver volume at month 12 was 33.8% (p < 0.001, n = 12). Most TEAEs were of mild/moderate severity.

Long-term effectiveness and safety of metreleptin in the treatment of patients with partial lipodystrophy. *Oral EA[1], Gorden P[2], Cochran E[2], Araújo-Vilar D[3], Savage DB[4], Long A[5], Fine G[5], Salinardi T[5], Brown RJ[2]. Endocrine. 2019 Jun;64(3):500-511. doi: 10.1007/s12020-019-01862-8. Epub 2019 Feb 25.*

Patients aged ≥ 6 months with PL, circulating leptin < 12.0 ng/mL, and diabetes mellitus, insulin resistance, or hypertriglyceridemia received metreleptin titrated to a mean of 0.124 mg/kg/day. Significant reductions in HbA1c (-0.6%), fasting TGs (-20.8%), FPG (-1.2 mmol/L), and liver volume (-13.4%) were observed in the overall PL population at month 12. In a subgroup of patients with baseline HbA1c ≥ 6.5% or TGs ≥ 5.65 mmol/L, significant (p < 0.05) reductions were seen in HbA1c (-0.9%), fasting TGs (-37.4%), FPG (-1.9 mmol/L), and liver volume (-12.4%). In this subgroup, 67.9% of patients had a ≥ 1% decrease in HbA1c or ≥ 30% decrease in fasting TGs, and 42.9% had a ≥ 2% decrease in HbA1c or ≥ 40% decrease in fasting TGs. Metreleptin was well tolerated with no unexpected safety signals. The most common TEAEs were abdominal pain, hypoglycemia, and nausea.

2. A clear understanding of disease progression and the experience of people with lipodystrophy and 3. Further data collection and research on disease progression and experience of patients who have not had metreleptin.

We have identified two main papers which describe disease progression in patients with lipodystrophy who have not had metreleptin treatment. These chart review studies confirm the burden of morbidity and premature mortality in patients with lipodystrophy. Whilst there is no new evidence available that metreleptin therapy reduces premature mortality it would seem logical that a significant improvement in metabolic surrogate markers eg of diabetes control (HbA1c) and non-alcoholic fatty liver disease could later translate into improved morbidity and mortality outcomes. Importantly we believe that the published studies reflect what would happen in UK patients as well. There is no reason to believe that the disease manifestations differ in different ethnic groups.

Comorbidities and Survival in Patients With Lipodystrophy: An International Chart Review Study. *Akinci B[1], Oral EA[2], Neidert A[2], Rus D[2], Cheng WY[3], Thompson-Leduc P[3], Cheung HC[3], Bradt*

P[4], Foss de Freitas MC[5], Montenegro RM[6], Fernandes VO[6], Cochran E[7], Brown RJ[7]. J Clin Endocrinol Metab. 2019 Nov 1;104(11):5120-5135. doi: 10.1210/jc.2018-02730.

A chart review study of 230 patients with confirmed GL or PL , who had never received leptin therapy. Patients were observed from birth to loss to follow-up, death, or date of chart abstraction. Five treatment centres were included (none in UK). Brazil (University of S~ao Paulo and the Federal University of Ceara´), Turkey (Dokuz Eylu¨ l University), and the United States (National Institutes of Health and the University of Michigan). Diabetes/insulin resistance was identified in 58.3% of patients. Liver abnormalities were the most common organ problem (71.7%), then kidney (40.4%), heart (30.4%), and pancreatitis (13.0%). Kaplan-Meier estimates of mean (SE) time to first organ abnormality were 7.7 years (0.9) in GL and 16.1 years (1.5) in PL (P < 0.001). Mean time to diabetes/insulin resistance was 12.7 years (1.2) in GL and 19.1 years (1.7) in PL (P = 0.131). Mean time to disease progression was 7.6 years (0.8) and comparable between GL and PL subgroups (P = 0.393). Mean time to death was 51.2 years (3.5) in GL and 66.6 years (1.0) in PL (P < 0.001).

Causes of death in patients with Berardinelli-Seip congenital generalized lipodystrophy. *PLoS One. 2018 Jun 8;13(6):e0199052. doi: 10.1371/journal.pone.0199052. eCollection 2018. Lima JG[1], Nobrega LHC[1], Lima NN[1], Dos Santos MCF[1], Silva PHD[1], Baracho MFP[1], Lima DN[2], de Melo Campos JTA[3], Ferreira LC[4], Freire Neto FP[4], Mendes-Aguiar CO[4], Jeronimo SMB[4].*

Death certificates and medical records of BSCL patients who died between 1997 and 2017 were examined. If the death certificate was incomplete or unavailable, medical records were reviewed, and if they were not available information was collected from the patient's relatives to understand how the death happened. None of the patients had received metreleptin therapy. Twenty patients (12 female and 8 male) died between 1997 and 2017. BSCL led to premature death, cutting the patients' lifespan by 30 or more years. The mean age at the time of death was 27.1±12.4 years (women 25.2±12.5 vs. men 29.9±12.6 years, p = 0.41). Life expectancy for the study population was 62.9±4.8 years. The causes of deaths were divided into three major groups: infections (7 patients, 35%), liver disease (7 patients, 35%), and other causes (acute pancreatitis, one patient; renal failure, three patients; sudden death/myocardial infarction, two patients). Three patients had pulmonary fibrosis. The potential number of years of life lost was 35.6±16.6 years.

Table 1. Causes of death and individual clinical features of patients with Berardinelli-Seip Congenital Lipodystrophy.

Patient#	Sex	BSCL type	Year of death	Age at death (years)	Reported main cause of death	Associated comorbidities
1	Male	NA†	1997	11	Liver disease	Diabetes
2	Male	NA	1997	21	Liver disease	Diabetes, kidney failure
3	Male	NA	1998	29	Respiratory insufficiency	Diabetes, pulmonary fibrosis
4	Female	NA	1999	27,1	Liver disease	Diabetes
5	Male	NA	2000	29	Gastrointestinal bleeding	Diabetes, cirrhosis
6	Female	NA	2002	9.3	Sepsis, pneumonia	Diabetes
7	Female	2	2005	39.7	Sepsis, pneumonia	Diabetes, cirrhosis, kidney failure
8	Female	NA	2009	27.6	Septic arthritis	Diabetes, cirrhosis, kidney failure (hemodialysis)
9	Female	2	2011	43.9	Kidney failure	Diabetes, cirrhosis, kidney failure, pulmonary fibrosis
10	Female	2	2011	21.5	Liver disease	Diabetes
11	Male	2	2013	41.7	Respiratory insufficiency	Diabetes, pulmonary fibrosis
12	Male	2	2013	20.4	Myocardial infarction*	Diabetes, acute pulmonary edema, arterial hypertension
13	Male	2	2013	52.6	Sudden death	Diabetes
14	Male	2	2014	25.8	Gastrointestinal bleeding	Diabetes, perforated gastric ulcer, kidney failure (hemodialysis)
15	Female	2	2014	18	Acute pancreatitis	Diabetes
16	Female	2	2014	31	Gastrointestinal bleeding	Diabetes
17	Female	NA	2015	2.1	Pneumonia	-
18	Female	2	2015	29.5	Sepsis, pneumonia	Diabetes, kidney failure
19	Male	2	2016	29.5	Kidney failure	Diabetes, amaurosis, hemodialysis
20	Female	2	2016	40.2	Kidney failure	Diabetes, amputation of leg, anemia

* Confirmed by necropsy.
Patients #1 and #2, and #3 and #11 are brothers. Patients #9 and #20 are sisters. Patient #6 is the sister of #14.
†NA = not available.

4. The substantial uncertainty about the model inputs. The utility values incorporated in the model were of high uncertainty because of the elicitation methods used.

We do not have expertise in designing models for predicting metabolic outcomes or health economic analyses however alternative suggestions to previous models include a model based on a composite of clinically meaningful outcomes including HbA1c, fasting triglycerides, onset of new diabetes, severity of fatty liver disease (as judged by liver function tests, clotting screen, presence/onset of cirrhosis, presence/detection of hepatocellular carcinoma, liver transplant), episodes of pancreatitis, episodes of symptomatic ischaemic heart disease, onset of new proteinuria, requirement for renal dialysis/transplant, foot ulcers etc. **Importantly, we think that the focus on hyperphagia is inappropriate though it does clearly cause significant distress to many patients, it is difficult to quantify and was not a formal endpoint in the NIH studies, so there just is not sufficient data on it and it would take years to accumulate now given that many patients are already on leptin therapy.**

Other comments

Expanded access programme data

We have provided extensive anonymous data to Amryt Pharmaceuticals for patients on the expanded access programme at Addenbrooke's Hospital. We have been as thorough as possible, but some historic data is not available as we do not have access to GP records or records from the NIH in patients who started metreleptin at the NIH many years ago. It should be noted that criteria for eligibility to this programme included partial lipodystrophy patients with relatively early metabolic problems eg an HbA1c in the non- diabetic range, and therefore would not necessarily include the patient group that we would suggest should now be eligible for metreleptin therapy. From our clinical experience we would like to propose

some starting/stopping guidance for 1. Patients with generalized lipodystrophy, and 2. Patients with partial lipodystrophy:

NSIR Service suggested guidance for starting and stopping metreleptin treatment

A specialist service review is mandatory pre metreleptin start and at 3,6,9,12,18 and 24 months post start and at least annually thereafter.

1. Generalised lipodystrophy

Suggested starting criteria generalised lipodystrophy

A specialist service review is mandatory pre metreleptin start

Starting criteria as specified in the therapeutic indications:

1. Confirmed generalised lipodystrophy (age over 2 years)
2. Optimal diet

No additional metabolic criteria

Suggested stopping criteria generalised lipodystrophy

At 6-9 months after starting metreleptin or anytime thereafter – after specialist service review

Stop metreleptin therapy if poor compliance/non-engagement with appointments

No metabolic stopping criteria

2. Partial lipodystrophy

Suggested starting criteria partial lipodystrophy

A specialist service review is mandatory pre metreleptin start

To start metreleptin therapy **all** criteria below must be met:

1. Confirmed partial lipodystrophy (age over 12 years)
2. Optimal diet
3. Maximal standard anti-diabetic and lipid lowering therapies including insulin therapy
4. HbA1c>7.5% (58mmol/mol) and/or fasting triglycerides >5.0mmol/l
5. Leptin concentration < 10ng/ml

Suggested stopping criteria partial lipodystrophy

At 6-9 months after starting metreleptin – specialist service review

1. Stop metreleptin therapy if there is poor compliance/non-engagement with appointments

2. Stop metreleptin therapy if there has NOT been an HbA1c reduction of at least 0.5% from baseline (eg from 8.0 to 7.5%, or 9.0 to 8.5%) or a fall in fasting triglycerides of at least 50% from baseline.

NB: The specialist service may agree to continue leptin therapy in occasional patients with partial lipodystrophy who have not met the above metabolic criteria but who are judged by the specialist service to have had other significant treatment benefits such as a very significant reduction in concomitant medication, significant improvement in fatty liver disease, and/or a significant improvement in quality of life due to for example a significant appetite reduction, or in whom a trial of dose escalation is thought to be required.

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: Tricia Tan

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 (for example doi: 10.1007/s12020-018-1589-1 and doi: 10.1007/s12020-019-01862-8) 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.

Some long-term safety data is now published for Metreleptin in this patient group, mainly based on the collective experience with the open-label study NIH 991265 which was extended to NIH 20010769 (doi: 10.1007/s12020-018-1589-1 and doi: 10.1007/s12020-019-01862-8). 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 occur in most patients.
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). This is the subject of a current trial (NCT04026178).
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) including autoimmune hepatitis and worsening of non-alcoholic steatohepatitis (doi: 10.1007/s12020-018-1589-1).

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.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Metreleptin for treating lipodystrophy: re-submission

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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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. Hannah Penton acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Irene Santi, Pim Wetzelaer, Steve Ryder 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 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
DSU	Decision Support Unit
EAP	early access programme
EClip	European Consortium of Lipodystrophies
eGFR	estimated glomerular filtration rate
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
IPW	inverse probability weighting
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 years gained
LYS	life years 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
NIH	National Institute for Health
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
RA	regression adjustment
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
SLR	systematic literature review
SmPC	summary of product characteristics
SoC	standard of care
TEAEs	treatment-emergent adverse events
TSD	Technical Support Document
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
ULN	upper limit of normal
USA	United States of America

Table of Contents

Abbreviations **3**

TABLE OF TABLES **9**

TABLE OF FIGURES **11**

1. SUMMARY **12**

1.1 Background 12

1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology 12

1.3 Critique of the decision problem in the company's submission 13

1.4 Summary of clinical effectiveness evidence submitted by the company 14

1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted 15

1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS 16

1.7 Summary of the ERG's critique of the value for money evidence submitted 18

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services 19

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health-related benefits 21

1.10 ERG commentary on the robustness of evidence submitted including strengths, weaknesses and areas of uncertainty 21

1.11 Summary of exploratory sensitivity analyses undertaken by the ERG 24

2. BACKGROUND **27**

2.1 Introduction 27

2.2 Description of health problem 27

2.2.1 Disease overview 27

2.2.2 Underlying course of the disease 29

2.2.3 Disease morbidity and mortality 29

2.3 Number of patients who will be covered by this particular therapeutic indication in the marketing authorisation each year, and the source of data. 31

2.4 Life expectancy 32

2.5 Impact on patients' health-related quality of life (HRQoL) 32

2.6 Current service provision 33

2.7 Description of the technology under assessment 33

3. CRITIQUE OF THE COMPANY'S INTERPRETATION OF THE DECISION PROBLEM 35

3.1 Introduction 35

3.2 Adherence to the decision problem 35

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope 39

3.3.1 Population 39

3.3.2 Interventions 40

3.3.3 Comparators 40

3.3.4 Outcomes 41

3.3.5 Cost to the NHS and PSS, and value for money 41

4. IMPACT OF THE NEW TECHNOLOGY – CLINICAL EFFECTIVENESS 42

4.1 Critique of the methods of review(s) 42

4.1.1 Searches 42

4.1.2 Inclusion criteria 43

4.1.3 Critique of data extraction 44

4.1.4 Quality assessment 44

4.1.5 Evidence synthesis 45

4.2 Critique of trials of the technology of interest, their analysis and interpretation 49

4.2.1 Studies included in/excluded from the submission 49

4.2.2 Details of relevant studies not included in the submission 63

4.2.3 Summary and critique of company's analysis of validity assessment 63

4.2.4 Summary and critique of results 63

4.3 Summary of evidence presented in other submissions 96

4.4 Results of the ITC 97

4.5 Additional work on clinical effectiveness undertaken by the ERG 102

4.6 Conclusions of the clinical effectiveness section 102

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies 102

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes 102

4.6.3 Uncertainties surrounding the clinical effectiveness 103

5. VALUE FOR MONEY FOR THE NHS AND PSS 105

5.1 Introduction 105

5.2 Review of existing economic analyses 105

5.2.1 Searches 105

5.2.2 Review process and results 106

5.3 Exposition of the company's model 107

5.3.1 Economic evaluation scope 107

5.3.2 Model structure 109

5.3.3 Evidence used to inform the company's model parameters 114

5.3.4 Model evaluation 146

5.4 Headline results reported within the company's submission 146

5.4.1 Deterministic results of the company 147

5.4.2 Sensitivity analyses presented within the company's submission 147

5.4.3 Validation 151

5.5 Discussion of the available evidence relating to value for money for the NHS and PSS 153

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG 155

6.1 Introduction 155

6.2 Explanation of the ERG adjustments 155

6.3 ERG base-case results 156

6.4 Exploratory scenario analyses conducted by the ERG 160

7. COST TO THE NHS AND PSS AND OTHER SECTORS 163

7.1 Summary of submitted evidence relating to the costs to the NHS and PSS 163

7.2 ERG critique of the company's budget impact analysis 164

8. IMPACT OF THE TECHNOLOGY BEYOND DIRECT HEALTH BENEFITS AND ON THE DELIVERY OF THE SPECIALISED SERVICE 167

8.1 Summary of cost savings estimated within the CS 167

8.1.1 Proportion of costs or benefits which fall outside of the NHS and PSS 167

8.1.2 Societal costs 167

8.1.3 Costs borne by patients 167
8.1.4 Other carer costs 168
8.1.5 Impact of the technology on research and innovation 168
8.2 Staffing and infrastructure requirements associated with the use of the technology 169
9. DISCUSSION 170
9.1 Statement of principal findings – clinical effectiveness 170
9.2 Statement of principal findings – cost effectiveness 171
9.3 Strengths and limitations 171
9.3.1 Strengths of the CS 171
9.3.2 Weaknesses of the CS 172
9.4 Uncertainties 173
10. REFERENCES 176
Appendix 1 187

TABLE OF TABLES

Table 1.1: Summary of ITC, using IPW method 14

Table 1.2: ERG base-case results (discounted) 25

Table 3.1 Adherence to the agreed decision problem, as reported in the CS 36

Table 4.1 Data sources for the clinical effectiveness systematic review (as reported in CS) 42

Table 4.2 Eligibility criteria 43

Table 4.3 Summary of study methods, reproduced from Tables 14 and 15, CS 53

Table 4.4 Baseline characteristics for study NIH 991265/20010769, reproduced from Table 16, CS 57

Table 4.5 Baseline characteristics for study FH101, reproduced from Table 17, CS 58

Table 4.6 Baseline characteristics for Addenbrooke's EAP, reproduced from Table 18, CS 59

Table 4.7 Baseline characteristics for the GL/PL Natural History Study, taken from Table 25, CS 60

Table 4.8 Baseline characteristics for study NIH follow-up study, reproduced from Technical report[48] 62

Table 4.9 Glycaemic control and lipid metabolism results from NIH 991265/20010769 study 66

Table 4.10 Subgroup analyses of glycaemic control and lipid metabolism subgroup results from NIH 991265/20010769 study 69

Table 4.11 Glycaemic control and lipid metabolism, results from FH101 study 71

Table 4.12 Glycaemic control and lipid metabolism results from Addenbrooke's EAP 74

Table 4.13 Glycaemic control and lipid metabolism results from naïve comparison 76

Table 4.14 Hepatic enzymes results from NIH 991265/20010769 study 77

Table 4.15 Hepatic enzymes results from FH101 study 78

Table 4.16 Liver enzyme results from naïve comparison 79

Table 4.17 Adverse events: study NIH 991265/20010769 (safety analysis set) 85

Table 4.18 Adverse events: Study FHA101 (safety analysis set) 87

Table 4.19 On-study deaths, study NIH 991265/20010769 (safety analysis set) 92

Table 4.20 On-study deaths, study FH101 (safety analysis set) 93

Table 4.21 Mortality and cause of death data from the NIH follow-up study 93

Table 4.22 Mortality and cause of death data from the GL/PL Natural History Study 94

Table 4.23 Mean change in HbA1c at 12 months, metreleptin w/wo supportive care vs. supportive care 97

Table 4.24 Mean change in triglycerides at 12 months, metreleptin w/wo supportive care vs. supportive care 98

Table 4.25 Mean change in ALT at 12 months, metreleptin w/wo supportive care vs. supportive care 98

Table 4.26 Mean change in AST at 12 months, metreleptin w/wo supportive care vs. supportive care 99

Table 4.27 Incidence of pancreatitis, metreleptin w/wo supportive care vs. supportive care 99

Table 4.28 All-cause mortality, metreleptin w/wo supportive care vs. supportive care 100

Table 4.29 Summary of assessment of covariate balance following adjustment using IPW 101

Table 5.1 Data sources for the cost effectiveness systematic review (as reported in CS) 105

Table 5.2 Adherence to the reference case principles relevant to highly specialised technologies 107

Table 5.3 Summary of evidence sources used to inform key parameter groups in the company's model 114

Table 5.4 Baseline characteristics, patients with GL and PL 116

Table 5.5 Patient demographics by analysis population and type of lipodystrophy 117

Table 5.6 Clinical transition probabilities 121

Table 5.7 Probability of different cardiovascular events 125

Table 5.8 Implied relative efficacy of metreleptin versus SC on HbA1c 126

Table 5.9 Utility values used in the model 133

Table 5.10 Rescaled DCE decrements and prevalence of symptoms and complications 137

Table 5.11: Proportions of patients receiving each metreleptin vial size 139

Table 5.12: Unit costs for each component and total costs of a routine monitoring visit 140

Table 5.13: Annual costs for routine monitoring visits per treatment 140

Table 5.14: Medication costs for patients receiving supportive care only 141

Table 5.15: Assumed reductions in supportive care medication for patients with PL receiving metreleptin 142

Table 5.16: Assumed reductions in supportive care medication for patients with GL receiving metreleptin 142

Table 5.17: Unit costs for each component and total costs of a routine monitoring visit 143

Table 5.18: Overview of health states costs and their sources for the various sub-models 144

Table 5.19: Company base-case results 147

Table 5.20: Scenario analyses results 149

Table 6.2 Cumulative impact of the ERGs preferred model assumptions 157

Table 6.3 ERG probabilistic base-case results 159

Table 6.4 ERG scenario results 161

Table 7.1 Company budget impact analysis 163

Table 7.2 ERG budget impact analysis 165

Table 9.1: Summary of ITC, using IPW method 170

TABLE OF FIGURES

Figure 4.1: Unweighted survival curve and number at risk 100

Figure 4.2: Weighted survival curve and number at risk 101

Figure 5.1: Individual patient-level model structure 109

Figure 5.2: Pancreas sub-model structure 110

Figure 5.3: Liver sub-model structure 110

Figure 5.4: Cardiovascular sub-model structure 111

Figure 5.5: Kidney sub-model structure 112

Figure 5.6: Neuropathy sub-model structure 113

Figure 5.7: Retinopathy sub-model structure 113

Figure 5.8: Mean (SEM) change in HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24, 36 and 48 of metreleptin treatment in NIH studies 991265/20010769 in GL patients 119

Figure 5.9 - Mean (SEM) HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24 and 36 of metreleptin treatment (FAS population) in NIH studies 991265/20010769 in PL subgroup patients 119

Figure 5.10 One-way sensitivity analysis - ICER results 148

Figure 5.11 Probabilistic sensitivity analysis scatterplot company base case 148

Figure 5.12 Cost effectiveness acceptability curve 149

Figure 5.13: Survival of GL, female patients 151

Figure 5.14: Survival of GL, male patients 152

Figure 5.15: Survival of PL, female patients 152

Figure 5.16: Survival of PL, male patients 152

Figure 6.1 PSA scatterplot ERG base case 160

Figure 6.2 Acceptability curve ERG base case 160

1. SUMMARY

1.1 Background

The term lipodystrophy (LD) is used to describe a heterogeneous group of ultra-rare, progressive, chronic disorders associated with complete or partial loss of adipose tissue. The loss of adipose tissue and subsequent leptin deficiency and reduced fat storage capacity leads to numerous complications such as diabetes, cardiovascular disease, pancreatitis, liver damage, renal damage, hyperphagia and polycystic ovary syndrome leading to high morbidity, impaired quality of life and premature death.

There are four main types of LD namely congenital generalised LD (CGL), acquired generalised LD (AGL), familial partial LD (FPL) and acquired partial LD (APL).

CGL, also known as Berardinelli-Seip syndrome, is an autosomal recessive disorder with multiple genetic causes characterised by an almost complete lack of body fat and prominent muscularity starting at birth or in early childhood. Shortly after birth, patients develop insatiable hunger and show accelerated linear growth rates. Infants may develop hepatosplenomegaly and umbilical prominence or hernia.

AGL, also known as Lawrence syndrome, is more common in females. Patients are born with normal fat distribution but progressively lose fat affecting the whole body. The loss of adipose tissue occurring in childhood or adolescence, is preceded or followed by autoimmune or inflammatory manifestations. Three subtypes of AGL have been proposed namely (panniculitis, autoimmune, and idiopathic).

FPL is characterised by the regional loss of subcutaneous adipose tissue. Patients with FPL usually have normal body fat distribution up until puberty, when they develop progressive loss of fat in the arms and legs resulting in a peripheral muscular appearance, and variable fat loss in the abdomen and chest according to subtype. There are various subtypes of FPL, including FPL1 (Köbberling variety), FPL2 (Dunnigan variety), up to FPL7.

APL, also known as Barraquer-Simons syndrome, usually has a childhood or adolescent onset and is more common in females. APL is distinguishable from other LD syndromes by the unique cephalocaudal progression of subcutaneous fat loss observed. Subcutaneous adipose tissue loss begins in the face and subsequently spreads to the neck, upper extremities, thorax and abdomen. The lower extremities, lower abdomen and gluteal region do not exhibit lipoatrophy but rather accumulate excess adipose tissue.

1.2 Summary of submitted evidence on the nature of the condition and the impact of the new technology

The company submission (CS) summarises the limited evidence available evaluating health-related quality of life (HRQoL) in patients with LD and their families. A conference abstract was identified reporting an evaluation of HRQoL in LD patients from the Lipodystrophy Connect Register. Participants were given five surveys, including the PROMIS Global Health Short Form (SF) which was used to calculate an EQ-5D utility score. The estimated mean EQ-5D score for the LD syndromes population was 0.67, compared to a general population estimate of 0.866. 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.

The CS also cited evidence from two additional sources, namely the Lipodystrophy Patient and Caregiver Survey which measured the quantitative impact of the disease on quality of life using SF-36

and the Lipodystrophy Caregiver Disease Burden Survey which measured the quantitative impact of carer burden via the Zarit Caregiver Burden Interview (ZBI) using EQ-5D.

The main impacts of the condition on HRQoL are described as substantial impacts on emotional/psychological wellbeing, impaired physical appearance (extreme muscularity of limbs, hepatomegaly, abdominal extension, excessive facial hair, acanthosis nigricans skeletal facial features and severe body asymmetry), hyperphagia, reproductive issues, physical health and everyday life.

The main impacts on carer HRQoL were described as impacts in terms of emotional wellbeing, physical health and everyday life.

The CS described additional detrimental impact on HRQoL associated with the complications of lipodystrophy, namely; glucose control, triglyceride control, organ (liver, heart, kidney, pancreas) damage, retinopathy, neuropathy, amputation and chronic pain.

The main impact of the new technology is suggested in the CS to be restoration of patients' metabolic function leading to slowing, halting or even (in some cases) reversing disease progression and organ damage, and thus carrying the potential to greatly improve patients' quality of life and survival.

1.3 Critique of the decision problem in the company's submission

Metreleptin was granted a marketing authorisation under exceptional circumstances by the European Medicines Agency (EMA) on the 29 July 2018. Metreleptin is indicated, as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in LD patients:

- with confirmed CGL (*Berardinelli-Seip syndrome*) or AGL (*Lawrence syndrome*) in adults and children two years of age and above [referred to as generalised lipodystrophy (GL)]
- with confirmed FPL or APL (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control [referred to as partial lipodystrophy (PL)]

The license is consistent with the scope. There are, however, some discrepancies between the licensed population and the data used for the main effectiveness and cost effectiveness analyses i.e. the data used for the treatment group in the indirect treatment comparison (ITC). Specifically, although the company asserts that the PL subgroup (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is the PL population most reflective of the licensed indication, the entire PL population was used for the ITC. However, given that the treatment effect for the PL subgroup is greater than for the whole PL population, the Evidence Review Group (ERG) believes that the ITC results are likely to be conservative in this respect. There are also a number of patients in each of the GL and PL populations in the GL/PL natural history study (the source of comparator data for the ITC) who are below the licensed GL and PL age cut-offs of two years and 12 years, respectively. However, given that the inclusion of younger patients appears to be consistent with decreased severity, the ERG believes that the adjustment for confounding employed in the ITC is likely to have reduced the bias in favour of the comparator, although by how much is unclear.

There is ambiguity in the definitions of both the intervention and comparator, but it appears to be the case that the comparator is supportive care and the intervention is metreleptin plus a reduced amount of supportive care, where supportive care is lipid-lowering and anti-hyperglycaemic therapies. It also appears to be the case that lifestyle modifications include both diet and exercise and that these, by their omission from further explanation or costing in the economic model, are implicitly assumed to be

common to both intervention and comparator. This assumption is questionable in that there is potential for variation both in clinical practice and between sources of evidence for intervention and comparator.

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 baseline HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L).

- In study NIH 991265/20010769, mean change in HbA_{1c} to Month 12/last observation carried forward (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 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% (95% CI: -46.9 to -25.2, 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, indicated 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 ITC, which was performed using the inverse probability weighting (IPW) method in the base case of the CS provided the following results (See Table 1.1): a statistically significant difference in favour of metreleptin vs. standard care in terms of HbA1c, triglycerides and liver enzymes at 12 months, as well as the odds of pancreatitis. There was however a numerical advantage to standard care in terms of all-cause mortality, albeit not statistically significant. These results were consistent when other methods of adjustment i.e. multivariate regression and IPW+ regression adjustment (RA) were used.

Table 1.1: Summary of ITC, using IPW method

Outcome	ATE	Robust standard error (%)	95% CI	p-value
Mean change in HbA1c at 12 months	-1.52	0.38	-2.28 to -0.77	**<0.001***
Mean change in triglycerides at 12 months, mg/dL [mmol/L]	-915.30 [10.34]	225.95 [2.55]	-1358.15 to -472.44 [-15.35 to -5.34]	<0.001*
Mean change in ALT at 12 months	-44.13	11.06	-65.81 to -22.46	<0.001*

Outcome	ATE	Robust standard error (%)	95% CI	p-value
Mean change in AST at 12 months	-27.79	6.93	-41.38 to -14.20	<0.001*
Odds ratio, pancreatitis	0.94	0.026	0.89 to 0.98	0.01*
Hazard ratio, all-cause mortality	1.38	0.40	0.88 to 20.37 lower limit corrected by ERG)	0.42

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; w / wo, With or without; RA, regression adjustment.
*denotes significance at the p<0.05 level
[a]Provided in response to clarification.

1.5 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company submission (CS) and response to clarification provided sufficient details for the ERG to appraise the literature searches. The CS states that a systematic literature review (SLR) was conducted to search for trials of metreleptin and trials of relevant comparators.

A 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 to one year in single arm studies. There was limited reporting of the GL/PL natural history study, used to provide comparator data, although the ERG was able to obtain all of the available data from the technical report. The population of the GL/PL natural history was not comparable to the National Institute for Health (NIH) studies, as indicated by the differences in baseline characteristics and use of lipid lowering drugs and anti-diabetic medications. It is therefore difficult to assess the extent to which any apparent treatment effects are attributable to metreleptin.

A further substantive issue concerns the nature of the treatment effects reported. The CS focuses primarily on changes in surrogate outcome measures (e.g. HbA1c, triglycerides, hepatic enzymes) and includes very little information about any effects of treatment on patient-perceived symptoms and clinical outcomes e.g. hyperphagia and organ damage, other than pancreatitis.

The company has made attempts to mitigate the problem of lack of comparability between studies by the conduct of an ITC with a method of adjustment to control for confounding. This approach remains limited in that it is still primarily reliant upon surrogate measures of outcome i.e. HbA1c, triglycerides, alanine transaminase (ALT) and aspartate transaminase (AST), although acute pancreatitis and all-cause mortality were included. The methodology of the ITC was based on recommendations by the NICE Decision Support Unit (DSU) in the form of Technical Support Document (TSD) 17 and two different methods of adjustment, IPW and multiple regression analysis, were compared with a naïve comparison. An assessment that showed lack of normality of distribution of the outcomes provided some evidence to favour IPW over multiple regression analysis. There was also reasonable consistency between the IPW and the IPW+ RA methods. The difference the adjustment made vs. the naïve comparison varied between outcomes, but for all continuous outcomes and pancreatitis the treatment effect continued to favour metreleptin, although with a lower treatment effect for pancreatitis (odds ratio 0.94 vs. 0.2). For all-cause mortality, the treatment effect numerically favouring supportive care decreased relative to the naïve comparison, but with a rise in uncertainty, as reflected by a larger p value.

There is also some doubt as to the applicability of the NIH follow-up study to UK clinical practice. The Early Access Programme (EAP), which includes only UK patients at Addenbrooke's Hospital, has been running for over 10 years and does provide some additional longer-term evidence i.e. up to 36 months follow-up. Some discrepancies in the effects of metreleptin treatment were noted (particularly with respect to changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a change of -3.5 mmol/l (Addenbrooke's EAP, based only on patients for which both baseline and 12 month data were available) vs. -10.54 mmol/l (NIH follow-up). Indeed, the EAP figure is closer to that of the GL/PL Natural History study of -4.43 mmol/l. The change in HbA1c at 12 months was also lower in the EAP than in the NIH follow-up study. For example, for all patients, it was -1.94% HbA1c in the NIH follow-up study vs. the highest value, which was -1.5 % HbA1c, for GL patients in the Addenbrooke's EAP data. Given these discrepancies and the apparent worse HbA1c and triglyceride outcomes observed in the EAP patients, the ERG would therefore recommend consideration of the performance of the ITC using data from the EAP, particularly for HbA1c and triglycerides.

The CS also 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 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 hypoglycaemia, autoimmunity, and hypersensitivity.'

1.6 Summary of the evidence submitted to support the value for money of the treatment and cost to the NHS and PSS

The company conducted and reported an update of the economic, cost and resource use and HRQoL SLRs. The updated SLRs identified a single additional study for use in the submission. No relevant economic studies were identified in either the original or updated SLR and therefore a de-novo model was required.

The company presented a de-novo individual patient level simulation model in which outcomes for patients with GL and PL lipodystrophy treated with metreleptin were compared to those patients treated with established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes). The model consists of six Markov sub-models simulating the progression of disease on distinct organ systems affected by lipodystrophy including: pancreas, liver disease, cardiovascular disease, kidney, neuropathy and retinopathy. In each year-long cycle a patient is simultaneously in a single health state in each of the six sub-models or in the absorbing death state. The model included 100 annual cycles, representing a lifetime horizon, with the impact of treatment on the HRQoL of patients and carers included and costs calculated according to the NHS and personal and social services (PSS) perspective. Both costs and quality adjusted life years (QALYs) were discounted at 3.5%.

Baseline patient characteristics, including age and proportion female were taken from the NIH studies. The PL characteristics were based on the PL subgroup from the safety analysis set of the NIH studies, rather than the overall PL group or the full analysis set. The PL subgroup has more severe metabolic abnormalities than the overall PL group.

Patient transitions through each of the sub-models were mostly determined by transition probabilities from the literature, in populations relevant to each sub-model condition, which were adjusted using

surrogate outcomes such as HbA1c, AST\ALT to account for the reduction in risk of organ complications associated with metreleptin. The pancreas model estimated the risk of pancreatitis in each treatment group directly from the ITC. In the liver model, an estimated risk reduction in liver disease complications in metreleptin-treated compared to standard of care (SoC)-treated patients was estimated from the Delphi Panel (with reduction in AST\ALT levels used estimated from the ITC used in a scenario). In the remaining four sub-models, HbA1c levels were used to adjust the risk of organ complications in metreleptin patients. Since the ITC for HbA1c could not be estimated separately in GL and PL patients, the naïve change in HbA1c from baseline from the NIH studies was used to determine efficacy. These adjustments in the risk of organ-complications in lipodystrophy patients taking metreleptin were assumed to continue long-term while still taking metreleptin and also post-discontinuation.

Stopping rules were incorporated into the model in order to stop metreleptin treatment in patients who were not experiencing sufficient benefit to make treatment worthwhile. Additionally, patients were assumed to discontinue at an annual rate of 1.50% for GL patients and 3.86% for PL patients, based on the discontinuation rate for treatment non-compliance from the NIH studies.

The risk of mortality runs separately alongside the various sub-models. All-cause mortality was sourced from UK Life tables available from the Office for National Statistics. Risk of mortality in lipodystrophy patients was assumed not to fall below that of the UK national life tables as it is assumed that a patient with no complications would have a similar risk of death to that of the general population. When patients occupied several different organ complication states which would inflate the risk of mortality past that of all-cause mortality, these mortality risk inflators from the separate models were aggregated using a conservative approach (selecting the highest individual risk of death across all organ systems) to create a single probability of death. For a cycle in which a patient dies, the effect of costs and QALYs are reduced by half and reduced to zero from the subsequent cycle onwards.

Adverse events were not included in the model as the company anticipated that their impact on costs and utilities would be minimal as they were mild or moderate in their severity and occurred at a low frequency and the impact of organ complications are already accounted for in the organ sub-models, which in turn impact cost and utilities.

In the model, patients experienced utility decrements due to organ complications. These decrements, with the exception of pancreatitis were sourced from the literature in relevant populations to each of the organ models. The decrement for pancreatitis was sourced from the discrete choice experiment (DCE) study which was used to estimate utility values for various lipodystrophy symptoms/complications in the original appraisal. The company also accounted for the impact of metreleptin on lipodystrophy specific symptoms which were assumed not to be accounted for in the organ sub-models such as hyperphagia, polycystic ovary syndrome (PCOS), inability to work and impaired physical appearance. This was modelled as a differential in utility of 0.12 between patients receiving metreleptin and standard of care (SoC), with the 0.12 differential also based on the DCE study. A disutility due to caring was also modelled for carers of patients receiving SoC. This disutility was estimated using the EQ-5D in a small group of carers of lipodystrophy patients. The number of carers per patient was estimated from a survey of carers of lipodystrophy patients, which showed that on average, the patients included had 1.67 carers. This was rounded to two carers per patient in the company base-case. The company assumed that if a patient discontinued from metreleptin, 50% of the 0.12 treatment differential and 50% of the benefit to carers was maintained post-discontinuation over the patient's remaining lifetime. All utility decrements were applied to age-specific UK general population EQ-5D norms.

In the model, company estimated drug acquisition costs, routine monitoring costs, supportive care costs and the costs of lipodystrophy-related organ complications. Drug administration costs for metreleptin, which would consist of the costs for home delivery and self-administration training, were not included since these costs will be funded by the company at no additional cost to patients or the NHS. Metreleptin dosage assumptions were based on data from the Early Access Programme and supportive care costs were based on the NIH studies. Routine monitoring costs were based on Delphi panel estimates. Costs of organ complications were usually identified in previous NICE guidelines or technology appraisals.

1.7 Summary of the ERG's critique of the value for money evidence submitted

The CS provided sufficient details for the ERG to appraise the literature searches, although several errors were identified in the searches and the grey literature search was not entirely transparent. The inclusion exclusion criteria were mostly appropriate although the HRQoL SLR excluded data from HRQoL measures not scaled between 0-1 for QALY estimation. This exclusion could have resulted in HRQoL data which could have been mapped to a preference-based measure for QALY estimation being missed. The updated SLRs identified a single additional study for use in the submission, which is thought to be relevant to the HRQoL section, however reporting of results of each specific SLR was not entirely clear.

The NICE committee had expressed concerns about the previous two economic models submitted in relation to this appraisal as they felt that they did not reflect disease progression of lipodystrophy over time. The committee acknowledged that evidence in the area of lipodystrophy was sparse but noted that metabolic, surrogate outcomes could be used to extrapolate outcomes in the model, and a diabetes or fatty liver model basis would be more appropriate to use as the basis for the model. The submitted model structure does reflect those suggestions by the committee and is an improvement on previous submissions as it is better structured to account for the potential progression of complications related to lipodystrophy over time. However, it remains predicated upon the assumption that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but different underlying disease states. This is an area of considerable uncertainty.

In the economic model, there is a lack of consistency in the subgroups of lipodystrophy patients used to estimate different parameters, particularly for PL patients. Two different subgroups of PL patients are defined in the NIH studies; PL overall and PL subgroup. The PL subgroup represents a subgroup of the PL overall patients who have at least 6.5% HbA1c level at baseline. Therefore, this PL subgroup represents a more severe group as they are more at risk of organ damage. The company used the PL overall group to estimate the ITC, but the PL subgroup to estimate other model inputs for PL patients from the NIH studies, included baseline characteristics, baseline levels of metabolic surrogates and changes from baseline of HbA1c. It is unclear in practice whether metreleptin will be given to all PL patients, or only those who meet the criteria for the PL subgroup. This treatment decision should be clear and reflected clearly in the model parameters: otherwise it is unclear to what extent model results reflect those PL patients who will receive metreleptin in practice.

The inputs used to determine transition probabilities in each treatment group in the model are subject to some uncertainty. With the exception of the pancreas model, none of the transition probabilities underlying the organ sub-models were estimated in lipodystrophy patients as the sub-models were representative of patients with diabetes and liver disease. Therefore, we cannot be sure how representative these transition probabilities are for metreleptin patients. Additionally, the only sub-model in the company base-case that made use of the ITC was the pancreas model. The reduction in the risk of liver complications was estimated from the Delphi panel, rather than from the ITC of AST/ALT

data from the NIH studies in the company base-case. It is unclear why expert opinion was preferred to patient data in this case. In the four remaining sub-models, naïve change from baseline data from the NIH studies was utilised rather than comparative data for change in HbA1c from baseline. This naïve approach limits the reliability of the estimated efficacy of metreleptin in the model.

The assumptions regarding the long-term efficacy of metreleptin, both while still taking metreleptin and post-discontinuation are also questionable. The CS only provided change in HbA1c from baseline data up to four years in GL and three years in PL patients (both with substantial patient drop out over time). No data was provided on the efficacy of metreleptin post-discontinuation and yet continued long-term post-discontinuation efficacy was assumed across all sub-models. This assumed long-term post-discontinuation efficacy cannot be substantiated without data.

The ERG considers that Grade 3 and 4 adverse events should have been included in the model for completeness.

Data on disutilities related to organ complications used in the model are mostly obtained from literature in non-lipodystrophy populations and therefore it is unclear how representative they are of lipodystrophy patients. The few utilities which are specific to lipodystrophy patients, including the treatment differential between metreleptin and SoC from symptoms such as hyperphagia, PCOS and inability to work were obtained from a single DCE study from the original submission, which was associated with substantial limitations. Therefore, the patient utility estimates used the model are also subject to uncertainty.

The disutility due to caring was estimated using the EQ-5D in a small group of carers of lipodystrophy patients. This represents a good estimate of disutility from an appropriate source, however the final value used in the model did not match the calculations described. The number of carers per patient was estimated from a survey of carers of lipodystrophy patients, which showed that on average, the patients included had 1.67 carers. The company base-case assumes two carers per patient as this average value was rounded up. However, the ERG believes that this overestimates the number of carers per patient and therefore the disutility due to caring per patient.

As in the organ models, a partial continued treatment effect in terms of the management of lipodystrophy symptoms including hyperphagia was assumed post-discontinuation from metreleptin. No evidence was presented to suggest that metreleptin had a continued impact on symptoms such as reduction in hyperphagia, PCOS, inability to work and impaired physical appearance.

The ERG considered that, given the data available, the implementation of costs in the model was appropriate.

The ERG identified several errors and inconsistencies in the company model, beyond those already described including: the number of baseline events entered in the model was inconsistent with the NIH data; in the neuropathy model, the company had incorrectly calculated several risk ratios (RRs); the incremental cost-effectiveness ratios (ICERs) presented in the model were incorrectly calculated as well as the calculation of the overall gender split in the results sheet.

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 company states that the majority of costs and health outcomes are expected to be captured within the economic analyses presented with treatment and management costs borne primarily by the NHS and PSS. However, the ability to attend school and the work/productivity loss associated with lipodystrophy

can be substantial. Most patients are affected from birth due to genetic/familial disease, with symptoms manifesting in childhood. These symptoms can lead to impaired or complete inability to work or attend school. The disease burden in childhood means that carers/families are also heavily affected. Post-childhood, lipodystrophy has also been shown to considerably impact patients' independence and ability to work and study, which can also impact on carers. While estimates on the impact of lipodystrophy on productivity are not available, the costs of reduced productivity at work (due to people with diabetes not working because of death or poor health or working at a lower level of productivity) are estimated at nearly £9 billion.

The company provided some data relating to the impact of metreleptin on the education and productivity of patients and carers. Of the 114 patients treated with metreleptin at the NIH, 35% had one caregiver not working or only working part time to support them due to their disease prior to metreleptin initiation compared to 7% following metreleptin initiation. In the lipodystrophy caregiver burden survey, 43% of respondents answered that they had had to either give up their work/study, reduce their hours, change their type of work/study or retire early due to caring responsibilities. Balancing carer responsibilities alongside other responsibilities can also leave carers strained for personal and social time, including time spent with other family members. 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 and among 64 non-adult patients treated with metreleptin, 59.4% had impaired school attendance. Therefore, productivity as well as HRQoL, both for patients and carers is expected to substantially improve with effective therapy.

Outside of the NHS and PSS, metreleptin is expected to reduce costs to local authority and education bodies. The substantial burden of lipodystrophy on young patients means they may require substantial additional support at school. In the UK, the schools, local authorities, health professionals, commissioners and other support services work together to ensure that children with medical conditions receive a full education. 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. The current burden on local authority and education bodies, as well as the improvement due to metreleptin is currently unquantified.

Metreleptin is also expected to impact on costs borne by patients and carers. These costs include travel expenses for bi-annual visits to Addenbrooke's Hospital as well as additional travel costs incurred to local centres post and prior to diagnosis e.g. to general practitioners or secondary care providers. Addenbrooke's is the only specialist centre in the UK and therefore overnight accommodation may be required for those travelling further. Metreleptin is administered subcutaneously and can be self-administered, which avoids unnecessary travel expenses and additional time off work required to travel to hospital for treatment. Other potential costs may include fertility treatment and cosmetic treatment, which are not always reimbursed by the NHS.

In terms of the impact of the technology on research and innovation, the company state that during the development of metreleptin, they have engaged in a comprehensive evidence generation programme to strengthen the evidence base on the understanding of lipodystrophy and the clinical effectiveness of metreleptin. The company also state that they are committed to continue to support such evidence generation, and hope that based on reimbursement in the UK, it will be able to continue to support the lipodystrophy community in the future via plans for enhanced data collection and patient registries. The European Consortium of Lipodystrophies (EClip) registry aims to compile data on the natural history of each different sub-group of lipodystrophies in patients not exposed to metreleptin, their comorbidities, treatment options used and medical and quality of life. Additionally, the Addenbrooke's Hospital EAP has set-up an enhanced data collection for patients receiving metreleptin from the

anticipated date of NICE issuing a positive recommendation for the use of metreleptin in January 2021 which includes the introduction of new outcomes and timeframes to be collected including ALT, AST, platelet count and estimated glomerular filtration rate (eGFR).

The company state that metreleptin is the first and only licensed medicine for the treatment of lipodystrophy which targets the underlying cause of the disease (leptin deficiency) and provides a step-change in the management of this severe debilitating disease. As a result, metreleptin has the potential to dramatically improve patients' lives via slowing disease progression, which has not been achievable before. However, ground-breaking advances in healthcare such as metreleptin are only meaningful when they reach the people who need them. Reimbursement of metreleptin would enable the company to continue to invest in the vital innovation and collaboration required to meet unmet patient and health system needs in the future.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health-related benefits

The ERG agree that the majority of costs and health outcomes have been included in the economic analyses within the appraisal. The ERG also agrees that the improvement of symptoms in patients taking metreleptin will likely reduce costs to other sectors such as education and improve ability to work and productivity. However, quantitative data on the likely extent of savings in these sectors and the impact of improvements in these areas on patients and carers are not available.

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 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 company has used the best available evidence on both metreleptin and standard care in the form of the NIH follow-up and the GL/PL natural history study respectively to perform an ITC.
- The ITC has been performed using a number of recommended methodologies, in order to test the robustness of each of these methodologies.
- The economic model is better structured to capture the progressive impact of lipodystrophy on affected organ systems and uses previously validated organ models and metabolic surrogate outcomes to predict final outcomes in lipodystrophy patients, as suggested by the committee in the previous appraisal.

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 on clinically important outcomes such as organ damage to the liver, heart and kidneys. The ITC only estimated the effects of metreleptin, for a period no longer than 12-months, on surrogate outcomes, with the exceptions of all-cause mortality and pancreatitis.
- The CS lacks information about the effects of metreleptin treatment on the important patient-perceived outcome of hyperphagia.

- The study details and results for the NIH follow-up study and the GL/PL natural history study, which were used to inform the ITC and the cost effectiveness modelling, were not included in the clinical effectiveness section of the CS.
- The CS lacks information about UK lipodystrophy patients. Although data from the Addenbrooke's EAP were included in the clinical effectiveness section of the CS, 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.
- Participants in the NIH follow-up study and the GL/PL natural history study were not comparable and it is not clear that the ITC reported in the CS was adequate to account for the apparent differences. In particular, it is unclear that sufficient relevant baseline characteristics were included to perform the adjustment.
- Many of the transition probabilities and utility values used in the organ sub-models are taken from the literature and are estimated in non-lipodystrophy populations. It is unclear to what extent these input values are generalisable to lipodystrophy patients.
- The company reported that the ITC could not be performed separately for GL and PL patients and therefore the ITC was only used in the pancreas and liver sub-models (although the company chose to use estimates of treatment effectiveness from the Delphi panel rather than the ITC in their base-case in the liver model). All other transition probabilities were taken from the literature and adjusted using HbA1c levels. Baseline and reduction in HbA1c due to metreleptin were estimated from naïve analysis rather than the ITC. Therefore, the ITC had a very minor role in the economic model. This naïve approach limits the reliability of the estimated efficacy of metreleptin in the model.
- The ITC used data from the PL overall group in the NIH studies, whereas patient characteristics used to estimate patient characteristics and outcomes in the rest of the model were from the PL subgroup, who were more metabolically severe. It is not clear which PL group the company intends to treat with metreleptin in clinical practice, but model inputs should have consistently reflected the group who are expected to receive metreleptin in clinical practice.
- The company assumed long-term continued efficacy of metreleptin post-discontinuation in terms of both HbA1c, risk reduction of liver disease progression and QoL. However, no evidence was presented regarding the post-discontinuation efficacy of metreleptin in any of these areas and therefore these assumptions could not be substantiated.
- The few utility values available from lipodystrophy patients are from a single DCE study which is associated with substantial study design issues, making the resulting utility values very uncertain
- Several errors had to be corrected in the model including: the average number of carers per patient, the number of pancreatitis events at baseline in the NIH studies, the calculation of some RRs in the neuropathy sub-model and the calculation of the final ICER in the model.

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 NIH 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 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 also included some information on newly emergent (on metreleptin treatment) lipodystrophy characteristics in patients with no evidence of these characteristics prior to metreleptin initiation. 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 HbA1c and triglycerides on metreleptin treatment. However, 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 (88%) developed antibodies to metreleptin. 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. These cases raise concern that development of neutralising antibodies to metreleptin could impair metabolic control and immune function.

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 natural history study, used to provide comparator data for the ITC has a population which is not comparable to those included in the metreleptin intervention studies. The company have therefore performed adjustments to control for confounding, but with only three covariates and with varying degrees of success with regards to balancing those covariates. Furthermore, even after adjustment (and using several different adjustment methods), survival was worse with metreleptin, albeit not statistically significantly.

It is unclear what criteria will be used to determine which patients with PL will receive metreleptin treatment. The EMA marketing authorisation, for PL, is for adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. The CS indicates that the company considers that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is the PL population most considered to best reflect the licensed indication. Leptin levels were part of the PL subgroup definition in NIH studies 991265/20010769, via the inclusion criteria (NIH 2001769: <12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years; NIH 991265: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males). The PL subgroup population in the Addenbrooke's EAP (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is therefore similar to that in the NIH studies 991265/20010769. It should be noted, however, that some PL patients who did not meet these baseline metabolic criteria have been treated in the Addenbrooke's EAP.

In the economic model, there is a lack in the subgroups of lipodystrophy patients used to estimate different parameters, particularly for PL patients. Two different subgroups of PL patients are defined in the NIH studies; PL overall and PL subgroup. The PL subgroup represents a subgroup of the PL overall patients who have at least 6.5% HbA1c level at baseline. Therefore, this PL subgroup represents a more severe group as they are more at risk of organ damage. The company used the PL overall group to estimate the ITC, but the PL subgroup to estimate other model inputs for PL patients from the NIH studies, included baseline characteristics, baseline levels of metabolic surrogates and changes from baseline of HbA1c. It is unclear in practice whether metreleptin will be given to all PL patients, or only those who meet the criteria for the PL subgroup. This treatment decision should be clear and reflected clearly in the model parameters, otherwise it is unclear to what extent model results reflect those PL patients who will receive metreleptin in practice.

Another area of uncertainty in the model is the extent to which lipodystrophy patients will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions. The model structure is certainly an improvement on previous rounds of this appraisal as it is able to use previously validated organ models and surrogate metabolic outcomes to estimate progression of organ damage and final outcomes in lipodystrophy patients. However, the generalisability of the populations used to estimate transition probabilities within each organ sub-model from the literature to lipodystrophy patients cannot be verified.

Similarly, data on utilities are mostly obtained from literature in non-lipodystrophy populations. The few utilities which are specific to lipodystrophy patients are obtained from a single DCE study from the original submission which is associated with substantial limitations and therefore utility estimates used the model are also subject to uncertainty.

A key area of uncertainty in the model is the long-term efficacy of metreleptin, both while it is still being taken and post-discontinuation. As outlined in the clinical effectiveness section, there is little evidence of the long-term effectiveness of metreleptin in patients continuing treatment. However, a key driver of cost effectiveness results is the assumption made regarding the post-discontinuation efficacy of metreleptin. The company assumed long-term continued efficacy in terms of HbA1c levels, risk reduction in liver complications and partial lifetime QoL benefits for patients and carers after metreleptin discontinuation. However, no data was provided in the submission on these outcomes post-discontinuation and therefore this remains and important area of uncertainty.

1.11 Summary of exploratory sensitivity analyses undertaken by the ERG

In response to errors in the company submission or assumptions which the ERG did not agree with, the ERG made the following changes to the company base-case:

1. The company scenario for the average number of carers assumed a value of 2 instead of the average of 1.67 from the Lipodystrophy Caregiver Burden Survey. This was corrected.
2. A disutility for the burden of caring of 0.0986 was used in the company model, based on the difference between the average EQ-5D value of 0.8124 from the Lipodystrophy Caregiver Burden Survey and the UK EQ-5D general population norm at the average age of carers in the survey (43.7) of 0.911. However, a different set of EQ-5D general population norms, representative of the UK-England, obtained from the same source were used elsewhere in the model as age-adjusted baseline utilities from which all utility decrements were subtracted. For consistency the ERG prefers to calculate the decrement due to caring based on the same set of general population norms. The UK-England general population norm is 0.893 at the age of 43.7, which results in a disutility due to caring of 0.0806.In the neuropathy model, the company had calculated RRs, assuming from odds ratios (ORs), however the values assumed to be ORs were in fact hazard ratios (HRs). The calculation of RRs was corrected to account for this.
3. The number of pancreatitis events from baseline was entered into the model as 45 but the data provided says there were 30 events. This was corrected.
4. The company adjusted transition probabilities in the liver model for treated patients using an RR estimate from the Delphi panel instead of the ALT/AST data available. The ERG prefers to use available data rather than expert opinion in this case.
5. The way that HbA1c was modelled meant that patients receiving metreleptin received the full treatment benefit in terms of a drop in HbAc1 upon treatment initiation. Thereafter, all patients in the model (whether on treatment with metreleptin, discontinued from metreleptin or receiving SoC) received an annual increase in HbA1c of 0.15%. Therefore, discontinuation had no impact on efficacy in the four organ sub-models using HbA1c to determine transition

probabilities. No evidence was provided of the efficacy of metreleptin post-discontinuation. This assumption was therefore considered unrealistic. As per TA315, the ERG modelled a reversal of the treatment effect on HbAc1 in the cycle after discontinuation to remove this assumption of long term continued treatment effect post metreleptin discontinuation.

6. The company also assumed long term treatment benefit post-discontinuation in the liver model. The ERG removed this assumption as no evidence was provided of post-discontinuation efficacy in terms of the liver.
7. The company model also assumed that 50% of the QoL treatment differential between metreleptin and SoC (assumed to cover issues such as hyperphagia, ability to perform work/schoolwork, physical appearance and PCOS) were maintained after discontinuation from metreleptin for patients and carers over the patient's remaining lifetime. No evidence was represented demonstrating a continued treatment effect in terms of hyperphagia, ability to perform work/schoolwork, physical appearance and PCOS after discontinuation and therefore this assumption was removed by the ERG.
8. In their base-case the company assumed discontinuation rates from the NIH trials based on non-compliance only of 1.5% and 3.86% in GL and PL patients respectively. These rates remained constant over time in the model. However actual discontinuation was higher in the trials. In Part 2 of the clarification response, the company provided final evaluation decision (FED) discontinuation rates of 8.93% in year 1, 5.63% in years 2-9 and 2.04% in years 10 onwards. This closer reflects the discontinuation observed in the first year of the NIH trial and the decline in discontinuation over time seems plausible. Therefore, the ERG used these rates in their base-case.
9. Given the higher rates of discontinuation adopted in the ERG base-case, the company's option to manually assume that an additional 10% of PL patients stop treatment (which was implemented by the company in order to align model discontinuation rates for PL patients with those expected by clinical experts) was turned off.

These changes form the ERG base-case. The results of the ERG base-case are displayed below in Table 1.2. Overall, across both types of lipodystrophy, metreleptin costs an additional [redacted] for a QALY gain of [redacted], resulting in an ICER of £241,531 per QALY gained compared to SoC. Incremental costs were higher in GL patients than PL patients, but this was outweighed by higher incremental QALYs in GL patients, resulting in a low ICER of £201,261 compared to £289,424 in GL and PL patients respectively.

Table 1.2: ERG base-case results (discounted)

Subgroup	Incr. costs (£)	Incr. LYGs (not discounted)	Incr. QALYs	ICER versus baseline (£/QALY)
GL	[redacted]	[redacted]	[redacted]	£201,261
PL	[redacted]	[redacted]	[redacted]	£289,424
Overall	[redacted]	[redacted]	[redacted]	£241,531

Abbreviations: ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALY = quality-adjusted life year

The ERG changes which had the largest impact on the ICER were removing the assumed 50% lifetime continuation of treatment benefits on patient and carer QoL post-discontinuation from metreleptin, amending the disutility due to caring and the average number of carers per patient and removing the post-discontinuation benefit in the liver model.

The probabilistic sensitivity analysis (PSA) yielded a probabilistic ICER of £242,987, which aligns quite closely with the deterministic result of £241,531. Note that in all PSA runs the incremental undiscounted QALY gain remained below 10. The scenarios which had the largest impact on results were assuming post-discontinuation treatment benefits for HbA1c, liver and 50% post-discontinuation benefit for the QoL of patients and carers (£174,492 per QALY gained) and assuming only one care giver per patient (£278,250 per QALY gained).

2. BACKGROUND

2.1 Introduction

In this report the Evidence Review Group (ERG) provides a review of the evidence submitted by the company in support of metreleptin, trade name Myalepta for the treatment of people with generalised or partial lipodystrophy. In this section, the ERG summarises and critiques the company's description of the underlying health problem as well as the company's overview of the current service provision. The information for this critique is taken from the CS.[1]

2.2 Description of health problem

2.2.1 Disease overview

The term lipodystrophy is used to describe a heterogeneous group of ultra-rare, progressive, chronic disorders associated with complete or partial loss of adipose tissue.[2] The absence of subcutaneous adipose tissue leads to a reduction in the level of endogenous leptin and a decrease in the individual's storage capacity of lipids, which accumulate ectopically in other organs.[3, 4]

Leptin deficiency, and the subsequent lack of adipose tissue, leads to the premature development of serious metabolic disorders such as diabetes (defined as HbA1c level >6.5%) or hypertriglyceridaemia (defined as triglyceride [TG] level >200 mg/dL, [>2.26mmol/L]) (2,5–7), which are generally difficult to manage as they do not respond to conventional treatment with hypoglycaemic and hypolipemic agents.[5] The CS states that the complications resulting from these metabolic disorders together with ectopic lipid deposition in various organs can lead to early development of cardiovascular complications and multi-organ damage that may become irreversible in organs such as the liver (hepatic steatosis, cirrhosis, liver failure), kidneys (nephropathy, proteinuria, renal failure) and pancreas (acute pancreatitis), leading to high morbidity, impaired quality of life and premature death.[2, 6, 7]

The CS states that the prevalence of the disease has been estimated worldwide at 0.2-1.0 cases/million for GL and 1.7-2.8 cases/million for PL.[8] In the UK, Addenbrooke's Hospital is the only Reference Centre for Lipodystrophy and has registered [redacted] patients with active lipodystrophy ([redacted] GL, [redacted] PL). The diagnosis of lipodystrophy which is based on the medical history, physical examination, distribution of body fat tissue and metabolic state of the patient is complex.[9] Given genetic testing or analysis of blood leptin levels can neither confirm nor discount the presence of lipodystrophy, the difficulty of diagnosis together with the low recognition of the disease (due to its rarity and low exposure to clinicians) leads to many patients being diagnosed late when the course of the disease is advanced and the multi-organ damage may be irreversible.[2, 5]

There is limited published data available on the incidence and prevalence of lipodystrophy in England and Wales. However, estimates based on EAP data from a decade of metreleptin use in UK clinical practice at Addenbrooke's Hospital indicate there are [redacted] lipodystrophy patients currently receiving metreleptin at Addenbrooke's Hospital under the EAP ([redacted] GL and [redacted] PL).

ERG comment: The ERG appreciates that prevalence data are limited in this area and that attempts have been made to search for epidemiology data. A systematic review was retrieved however there were significant flaws in the methodology of this review, which should be acknowledged.[8] The systematic review aimed to quantitatively estimate the prevalence of all LD, GL, and PL through a search of five electronic medical record (EMR) databases and a literature search. The search strategy was very limited and unlikely to retrieve all the relevant records. This observation is supported by the low number of records retrieved (n=621). Records that summarised cases of LD from countries outside of the European

Union were excluded. Consequently, the results from the literature review were not representative of the worldwide prevalence. The study estimated prevalence estimated using a three-step process.[8] Firstly, the total number of European cases identified for all LD (AGL + CGL + APL + FPL), GL (AGL + CGL), and PL (APL + FPL) was determined. Secondly, the total number of cases identified was multiplied by four, based on the assumption that only one quarter of patients have been reported. This assumption was based on a further study by one of the authors and no evidence was provided to support this assumption.[10] Thirdly, the total number of cases for all LD, GL, and PL (after adjustment for underreporting) was divided by the total European Union community population as of 2012 figure (507,751,512 people). This does not allow for the fact that not all countries may have reported patients and some countries may have a higher prevalence than others. The countries represented are not listed, the studies included are not listed and so the basis for estimating the prevalence in Europe is not clearly reported or transparent.

Lipodystrophy syndromes are categorised firstly by aetiology (i.e. genetic or acquired) and secondly by the distribution of adipose tissue deficiency (i.e. generalised, affecting the entire body, or partial). This leads to four main categories: congenital generalised LD (CGL), acquired generalised LD (AGL), familial partial LD (FPL) and acquired partial LD (APL).[1, 2]

Congenital generalised lipodystrophy

CGL which is also known as Berardinelli-Seip syndrome, is an autosomal recessive disorder with multiple genetic causes characterised by nearly a complete lack of body fat and prominent muscularity starting at birth or in early childhood.[1, 2, 10, 11] Shortly after birth, patients with CGL develop insatiable hunger and show accelerated linear growth rates.[1, 2, 10] Infants may develop hepatosplenomegaly and umbilical prominence or hernia.[10] Patients may also have phlebomegaly and acanthosis nigricans later in childhood.[2, 10] Further details of physical and clinical features and subtypes are listed in Table 4 of the CS.[1]

Acquired generalised lipodystrophy

CGL, which is also known as Lawrence syndrome, is more common in females (female: male ratio 3:1). Unlike CGL, patients with AGL are born with normal fat distribution but progressively lose fat affecting the whole body including palms and soles of the feet.[1, 2, 12] The loss of adipose tissue occurring in childhood or adolescence, is preceded or followed by autoimmune or inflammatory manifestations and three subtypes of AGL have been proposed namely (panniculitis, autoimmune, and idiopathic). In addition, lymphoma has been reported to be associated with AGL and an increased risk of malignancy in these individuals which may be attributable to autoimmune disease has been reported.[9] AGL appears to be more common in females (by a ratio of 3 to 1).[2] Further details of physical and clinical features and subtypes are listed in Table 4 of the CS.[1]

Familial partial lipodystrophy

FPL is characterised by the regional loss of subcutaneous adipose tissue. Patients with FPL usually have normal body fat distribution up until the beginning of, or after, puberty, at which point patients will develop the progressive loss of fat in the arms and legs resulting in a peripheral muscular appearance and variable fat loss in the abdomen and chest according to subtype.[5] There are various subtypes of FPL, including FPL1 (Köbberling variety), FPL2 (Dunnigan variety), up to FPL7, the causes and effects of which are described in Table 5 of the CS.[1]

Acquired partial lipodystrophy

APL, 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, 11] Subcutaneous adipose tissue loss begins in the face and subsequently spreads to the neck, upper extremities, thorax and abdomen.[1, 2, 11] The lower extremities, lower abdomen and gluteal region do not exhibit lipoatrophy but rather accumulate excess adipose tissue.[1, 2, 11, 13] Further details of physical and clinical features are listed in Table 5 of the CS.[1]

ERG comment: The CS gives a full and accurate account of physical and clinical features associated with the various types of lipodystrophy syndromes.

2.2.2 Underlying course of the disease

Subcutaneous adipose tissue loss is a primary feature of LD, regardless of the sub-type. Leptin is an essential metabolic hormone produced by adipose tissue which plays a crucial role in energy homeostasis, neuroendocrinology, and metabolism.[14, 15] The loss of adipose tissue and subsequent leptin deficiency and reduced fat storage capacity leads to numerous metabolic complications as illustrated in Figure 1 of the CS.[1]

The CS explains that adipose tissue is the body's single most important energy storage site,[1] with excess lipids being primarily stored in the form of triglycerides.[14, 16] With adipose tissue loss, storage capacity for triglycerides is easily exceeded, leading to ectopic fat accumulation in non-adipose tissue, including the musculature and organs such as the liver, heart, kidney and the pancreas, insulin resistance, hyperglycaemia, hard to treat diabetes and severe hypertriglyceridaemia. Excess triglycerides accumulate ectopically in non-adipose tissue, which may lead to direct lipotoxicity and patient morbidity at a young age.

Adipose tissue also plays an important role in energy metabolism and insulin sensitivity through the control of lipid metabolism and the secretion of leptin.[14] Figure 1 of the CS shows the consequences of adipose tissue loss namely hyperphagia, immunological and hormonal impairments, and metabolic dysfunction.[1]

The CS states that the multiple metabolic and endocrine issues caused by leptin deficiency which are often severe and can have potentially life-threatening consequences.[1]

ERG comment: The CS states: 'Leptin has multiple roles in normal physiology including the protection of peripheral tissues from lipotoxicity and regulating fatty acid metabolism.'[17] The reference given refers to a study of fatless mice. The ERG would suggest that the role of leptin in mice may not be directly comparable to the role in humans.

2.2.3 Disease morbidity and mortality

This section provides further information on the range of complications associated with lipodystrophy which include:

- Pancreas complications
- Liver disease
- Heart disease
- Renal disease
- Insatiable hunger and hyperphagia
- Physical appearance
- Precocious puberty and Infertility
- Premature mortality

2.2.3.1 Pancreatitis

The CS[1] states that patients with lipodystrophies are predisposed to developing acute pancreatitis,[10] which is associated with increased mortality.[18] This is supported by Akinci et al who reported that 12.5% of GL patients reported pancreatitis over their lifetime.[19] Furthermore, there is some evidence to suggest that hypertriglyceridaemia-associated acute pancreatitis may result in worse clinical outcomes than other acute pancreatitis associated aetiologies.[20]

ERG comment: The CS states: 'Similarly, baseline characteristics of the cohort in the QuaLip study reported that 17.91% of the adult population in the cohort (n=67) were diagnosed with pancreatitis. The NIH follow up study found that prior to metreleptin treatment 39.3% of patients had a diagnosis of acute pancreatitis, and after metreleptin treatment this number reduced drastically to only 0.9% of the patient population having a diagnosis of acute pancreatitis.' However, no references were given.

2.2.3.2 Liver disease

Liver disease, in terms of liver failure, gastrointestinal haemorrhage and hepatocellular carcinoma, is thought to be a major cause of mortality in lipodystrophy patients.[2] Clinical experts have highlighted that the liver disease complications experienced by LD patients are similar to those associated with non-alcoholic fatty liver disease (NAFLD).

A large retrospective review of liver damage in lipodystrophy found that the liver was the most commonly damaged organ.[21] Among metreleptin-treated patients (68 GL; 44 PL), 91.1% of GL and 72.9% of PL patients had liver damage prior to treatment. In metreleptin-naïve patients (56 GL; 122 PL), 94% of GL patients and 73% of PL patients had liver damage. In a recent study of lipodystrophy patients, liver abnormalities (including hepatic steatosis, hepatomegaly and cirrhosis) were the most common organ abnormality (overall sample n=230; 71.7%, GL subgroup n=81; 87.7% , PL subgroup n=149; 63.1%).[22]

ERG comment: The CS states: 'Ectopic fat deposition in the liver and muscle can progress to hepatomegaly, steatohepatitis, portal hypertension, cirrhosis and liver failure.'[23] The reference provided to support this statement was a conference abstract which examined the effect of metreleptin on liver volume and key metabolic parameters in pediatric patients with GL but does not provide support for a link between ectopic fat deposition in the liver and muscle and hepatomegaly, steatohepatitis, portal hypertension, cirrhosis and liver failure.

2.2.3.3 Heart disease

Leptin deficiency resulting from the loss of adipose tissue loss is associated with increases HbA1c levels and hard to treat diabetes and is also associated with cardiovascular disease, cardiomyopathy and heart failure as illustrated in Figure 2 of the CS.[1]

ERG comment: The CS states: 'Elevated triglyceride levels are a known risk factor for cardiovascular disease,'[24] however, the reference given describes the clinical and laboratory characteristics of a large series of patients with congenital generalised lipodystrophy and does not provide support for the link between elevated triglyceride levels and cardiovascular disease. The CS also states: 'Heart abnormalities, such as coronary heart disease, cardiomyopathy, and heart failure, have been reported to occur in 30.4% of lipodystrophy patients.' No reference is cited for this information.

2.2.3.4 Renal disease

The CS states: 'Kidney abnormalities are common in lipodystrophy patients as a result of ectopic fat accumulation in the kidneys and the lipotoxicity that occurs from this.'.[1]

A longitudinal medical chart review study of 56 GL patients found that kidney abnormalities occurred in 50% of patients, including kidney failure (7.1%) and nephropathy (42.9%).[19]. Proteinuria, a type of nephropathy, is a frequent finding in patients with lipodystrophy.[2, 25]

In a study of 230 GL and PL patients, kidney abnormalities were found in 40.4% of patients. Specifically, 32.2% experienced nephropathy, 4.3% chronic renal failure, 3.5% End Stage Renal Disease (ESRD), 0.4% kidney transplant, and 12.2% other (including haematuria, kidney stones, nephromegaly, renal hypoplasia).[22]

2.2.3.5 Insatiable hunger and hyperphagia

Patients with lipodystrophy, especially generalised forms, typically exhibit hyperphagia.[2] Leptin is a satiety signal, consequently low leptin levels send a starvation signal to the brain. Patients with lipodystrophy suffer from insatiable hunger which causes distress to themselves and caregivers. Hyperphagia leads to an increased caloric intake which worsens the metabolic situation and ectopic fat accumulation.[14]

2.2.3.6 Physical appearance

The partial and generalised loss of subcutaneous fat and abnormal fat distribution can have marked effects on the physical appearance of patients with GL and PL which causes distress and reduces quality of life.[26] Details of fat distribution and physical features across lipodystrophy type are described in the CS.[1]

2.2.3.7 Precocious puberty and Infertility

The CS states that leptin regulates secretion of gonadotropins and gonadal steroids which influence puberty and fertility. Leptin deficiency from lipodystrophy thus impacts hormonal balance such that oligo/amenorrhea, decreased fertility, and polycystic ovary syndrome (PCOS) are common in female PL patients. Additionally, early adrenarche, true precocious puberty, or central hypogonadism may occur in children with generalised lipodystrophy.[2]

2.3 Number of patients who will be covered by this particular therapeutic indication in the marketing authorisation each year, and the source of data.

The CS suggests that as some of these patients may have initiated metreleptin over a decade ago. Since the EAP has been running for over 10 years, the number of patients on the programme is a good indicator of the number of eligible patients in the England.[1] Clinicians from Addenbrooke's Hospital in England who are involved in the UK EAP were 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 six new patients each year would be eligible for metreleptin treatment (two for GL and four for PL). Section 13.1 of the CS shows the estimated number of new patients eligible for metreleptin in England over the next five years.[1]

ERG comment: It is unclear if all patients identified in the UK are included in the EAP. It is unclear what criteria will be used to determine which patients with PL will receive metreleptin treatment. The EMA marketing authorisation, for PL, is for adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.[27] The CS notes that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is the PL population most considered to best reflect the licensed indication. Leptin levels were part of the PL subgroup definition in NIH studies 991265/20010769, via the inclusion criteria (NIH 2001769: <12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years; NIH 991265: ≤8.0 ng/mL in

females and ≤6.0 ng/mL in males). The PL subgroup population in the Addenbrooke's EAP (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is therefore similar to that in the NIH studies 991265/20010769. It should be noted, however, that some PL patients who did not meet these baseline metabolic criteria have been treated in the Addenbrooke's EAP.

2.4 Life expectancy

The CS states that there is no evidence to indicate the life expectancy of lipodystrophy patients in the UK, although it is suggested that data from other countries are likely to be generalisable to the UK. The CS states: 'The complications of lipodystrophy are serious and have catastrophic consequences leading to premature mortality, occurring at young ages in some cases.'[1]

In a systematic review, the mean age of death was estimated to be 12.5 years for patients with CGL, 32.2 years for AGL, 27.8 years for FPL and 22.7 years for APL.[12]

An international chart review of patients with lipodystrophy reported the mean age of death to be 33.8 years for patients with GL and 53.9 years for patients with PL, demonstrating significant premature mortality. Contributing factors to death included cardiovascular events, liver disease and pancreatitis.[22]

ERG comment: The recently published systematic review, cited in the CS, 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.[12] The review included 519 patients with CGL, 86 patients with AGL, 124 patients with FPL and 124 patients with APL.[12] The geographic distribution of the studies included in this review was not clear, however, the review did 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.[12] Of 84 patients with AGL, nine 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.[12] For partial lipodystrophy, seven out of 98 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 (out of 124) 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).[12]

2.5 Impact on patients' health-related quality of life (HRQoL)

The CS (section 7.1, page 48) states that there is limited evidence available evaluating health-related quality of life (HRQoL) in patients with LD and their families. A conference abstract was identified 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.[28] 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 estimated mean EQ-5D score for the LD syndromes population was 0.67, compared to a general population estimate of 0.866.[28] 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.[28]

The CS also cited evidence from two additional interviews and surveys namely the Lipodystrophy Patient and Caregiver Survey which measured the quantitative impact of the disease on quality of life

was assessed via SF-36 and the Lipodystrophy Caregiver Disease Burden Survey which measured the quantitative impact of carer burden via the Zarit Caregiver Burden Interview (ZBI). Health-related quality of life was assessed through the EQ-5D.[26, 29]

The CS describes the main impacts on HRQoL of patients as substantial impact on emotional/psychological wellbeing, impaired physical appearance (extreme muscularity of limbs, hepatomegaly, abdominal extension, excessive facial hair, acanthosis nigricans skeletal facial features and severe body asymmetry), hyperphagia, reproductive issues, physical health and everyday life.

The main impacts on carer HRQoL were described in the CS in terms of emotional wellbeing, physical health and everyday life.

The CS described additional detrimental impact on HRQoL associated in with the complications of lipodystrophy, namely; glucose control, triglyceride control, organ (liver, heart, kidney, pancreas) damage, retinopathy, neuropathy, amputation and chronic pain,

ERG comment: The CS provided a standard deviation of 0.11 for EQ-5D score associated with LD (CS section 7.1, page 45). This value is not quoted in the conference abstract and so cannot be verified.[28]

2.6 Current service provision

The CS states that the current mainstay for the management of lipodystrophy is diet and lifestyle modification. The metabolic complications associated with lipodystrophy are currently managed in the NHS in England via the additional use of a combination of 'supportive care' therapies e.g. lipid-lowering and anti-hyperglycaemic therapies.

Metreleptin has not been launched in the UK and there are no other licenced treatments available for patients with lipodystrophy. 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)[30] is provided in the CS (CS, section 8.1.1, Table 9).

The CS states that the disease's heterogeneity means the clinical pathway of care can vary between patients with lipodystrophy in England.[1] Standard management of lipodystrophy requires a multidisciplinary team including diabetologists/endocrinologists, dieticians, specialist nurses, and if required specialists in psychological support and genetic counselling. Individualised decision-making is needed with close consultation among the patient, physicians, family members, and other carers. Initially, the standard of care comprises an energy-restricted diet to lower triglycerides and glucose. Dietary restriction may be challenging to achieve in some patients due to hyperphagia associated with leptin deficiency. In addition to diet management, drug treatments are aimed at treating complications such as diabetes (anti-hyperglycaemic treatments, such as metformin) and hypertriglyceridaemia (fibrates, statins).[1] Section 8.1.1.2 of the CS (pages 69-71) provides a description of the various management options including additional treatments for specific comorbidities (CS, section 8.1.1.2, Table 10)

2.7 Description of the technology under assessment

Metreleptin (methionyl recombinant human leptin) is an analogue of the human hormone leptin. Lipodystrophy is characterised by complete or partial loss or absence of subcutaneous adipose tissue. Adipose tissue plays a key role in energy metabolism and insulin sensitivity through the control of lipid metabolism, which is regulated via the secretion of leptin.[1, 31]

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,[32] 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.[32] 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.

3.2 Adherence to the decision problem

Table 3.1 presents a summary of the decision problem as set out in the NICE scope[32] and the company's adherence to this (based on information presented in Table 1 of the CS).[1]

Table 3.1 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	Adults and children above the age of 2 years with generalised lipodystrophy Or, adults and children above the age of 12 years with partial lipodystrophy, when standard treatments have failed This aligns with EMA regulatory approval – see Section 3.3.1.
Intervention	Metreleptin as adjunct to diet	No deviations from scope except that it is stated as additional to diet – see Section 3.3.2.
Comparator(s)	Established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes)	Supportive care – Table 1 in the CS states that: 'Diet lifestyle modifications are a mainstay of disease management irrespective of treatment, and therefore is considered distinct from supportive care.' – see Section 3.3.3.
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	As in scope except: No mention of infection and some re-interpretation: Improvement in metabolic abnormalities expressed as triglycerides Liver function (including cirrhosis) expressed as (ALT, AST, liver volume cirrhosis) Glucose control and diabetes (including complications of diabetes and need for diabetes therapies) expressed as HbA1c (glucose control) and diabetes (including complications of diabetes) Satiety expressed as Hyperphagia (satiety) See Section 3.3.4.

	Final scope issued by NICE	Deviations of submission from the scope
	Health-related quality of life (for patients and carers; including effects on appearance)	
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
Cost to the NHS and Personal Social Services (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 deviations from scope
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
Special considerations, including issues related to equality	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	Subgroups included in the model were identified based on the licensed 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

	Final scope issued by NICE	Deviations of submission from the scope
	Guidance will take into account any Managed Access Arrangements	
Related NICE recommendations and NICE Pathways	None	None
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.[33] 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.[34] 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.[35] Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/513157/NHSOF_at_a_glance.pdf	None

3.3 ERG critique of the company's adherence to the decision problem as set out in the NICE scope

3.3.1 Population

Metreleptin was granted a marketing authorisation under exceptional circumstances by the European Medicines Agency (EMA) on the 29 July 2018.[27] Metreleptin is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy patients:[27]

- with confirmed CGL (*Berardinelli-Seip syndrome*) or AGL (*Lawrence syndrome*) in adults and children two years of age and above [referred to as GL]
- with confirmed FPL or APL (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control [referred to as PL]

ERG comment: The license is entirely consistent with the scope.[32] The CS goes on to state that 'the anticipated date of UK availability is January 2021.' (p.31), although it is '…currently provided free of charge by a single centre at Addenbrooke's Hospital…The service specification is for insulin resistant diabetes, which covers lipodystrophy and includes the use of leptin replacement therapy.' (p.32)[32]

The ERG requested clarification in Question A12 of the clarification letter regarding whether the PL subgroup (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) was being treated as representing patients for whom standard treatments have failed.[36] The following information was also requested:

- the number of GL patients in each of the key studies (NIH 991265/20010769, NIH follow-up study, FHA101 and GL/PL Natural History study) who were under two years of age.
- the number of PL patients in each of the key studies (NIH 991265/20010769, NIH follow-up study, FHA101 and GL/PL Natural History study) who were under 12 years of age.

The company response was that the PL subgroup is representative of those patients for whom standard treatments have failed to achieve adequate metabolic control.[37] However, the ERG note that the population from which data were obtained for the ITC (see Section 4.1.5) was not the PL subgroup, but the whole PL population from the NIH follow-up study. This was confirmed in answer to question A36, the reason being given for not using the PL subgroup being '…sample size constraints.' (p.31).[37]

The number (percentage) of GL patients less than two years old was: 1 (1.5%) and 27 (33.3%) in the NIH follow-up and GL/PL natural history studies respectively.[37] The number (percentage) of PL patients less than 12 years old was: 2 (4.5%) and 15 (10.1%) in the NIH follow-up and GL/PL natural history studies respectively.[37] However, for the ITC analysis of HbA1c, the number of PL patients who were under 12 years old with complete HbA1c data was two patients from the NIH follow-up study and none from the GL/PL Natural History study. There does therefore seem to be a discrepancy between the patients included in the GL/PL natural history study and the licensed population. However, the company further point out that '…glucose metabolism derangements will rarely develop in GL patients under 2 years old…[and]…in PL patients under 12 years old.' (p.5)[37] This does seem to be consistent with the reduced severity of the patients in the GL/PL natural history study, as indicated by the baseline characteristics (See Section 4.2.2). The ERG has therefore concluded that these small discrepancies are of probably of little consequence.

3.3.2 Interventions

According to Table 2 and the EMA license, metreleptin is indicated as an adjunct to diet as a replacement therapy.[27]

3.3.3 Comparators

Since the license stipulates that metreleptin must be an adjunct to diet, diet must also be part of the comparator. Table 1 in the CS states that the comparator is 'supportive care' and asserts that this is different to diet and lifestyle modifications. This would imply that diet is common to both intervention and comparator. The question then arises as to what is meant by 'lifestyle modifications' and whether these are also common to both interventions and comparator such that the only aspect of the comparator, other than lack of metreleptin, that is different to the intervention is 'supportive care'.

There is no further clarification of what is meant by 'lifestyle modifications', although it seems that it can also be a catchall term for diet and exercise: 'Conventional therapeutic options include lifestyle modifications (diet and exercise),…' (p.73).[1] This is also indicated in Table 60 where diet and exercise are subheadings for lifestyle modifications. Indeed, exercise is supposed to be encouraged in those with GL or PL except, as reported on page 70, for the prohibition of strenuous exercise in those with cardiomyopathy or contact sports in those with severe hepatosplenomegaly and CGL patients with lytic bone lesions.[1]

'Supportive care' is defined on page 16 as: '…lipid-lowering and anti-hyperglycaemic therapies.' It is also indicated that 'supportive care' is what both GL and PL patients received in the GL/PL Natural history study (NHS). No further details are provided for this study. However, it is noteworthy that Table 16 shows that in the metreleptin studies, referred to as NIH studies 991265/200110769 not all patients were taking such medication at baseline. Indeed, as few as 51.5% of GL patients were on lipid-lowering medications at baseline. Not surprisingly as many as 96.8% of the 'PL subgroup' were on anti-diabetic medications, given that this is subgroup was defined as baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L. It is these NIH studies that inform the precise nature of supportive care, used to inform costs in the economic model, as reported in Section 12.3.6:[1]

- Insulin (assumed to be Intermediate or long acting insulin, combined with fast acting insulin in a 70:30 ratio)
- Oral antidiabetic medication: biguanides, thiazolidinediones and sulfonylureas
- Lipid Lowering Therapies: HMG CoA Reductase inhibitors and other lipid modifying agents
- Other concomitant medications: lisinopril and enalapril

However, although the classes of drugs that form supportive care were obtained from the NIH studies, it is unclear if the NIH studies were the source, other than for insulin where it is stated: 'The dose of insulin (number of units per day) was informed using baseline data from the NIH studies 991265/20010769' (p.201).[1] Indeed, the specific medication, form and strength were reported to have been determined using NHS prescription data.

Although 'supportive care' is used to denote the comparator in the economic model, in Section 12.3.6 it emerges that 'supportive care' is also common to the intervention with reductions in terms of patients able to discontinue or reduce dose (and the dose reduction) estimated by Delphi panel and reported in Tables 47 and 48.[1]

ERG comment: The ERG requested clarification on the level and nature of lifestyle modifications (diet and exercise) and lipid-lowering and anti-hyperglycaemic therapies in each of the metreleptin and GL/PL natural history studies as well as what would be expected in clinical practice.[36] The company responded by indicating the variability in experience of medication.[37] They also stated that in the NIH studies 991265/20010769 diet was neither prescribed nor recorded and neither was calory intake recorded. They stated that only baseline medication use was reported for the GL/PL study, for which they provided a table the data from which has been incorporated in Table 4.7 below.

There remains ambiguity in the definitions of both the intervention and comparator, but it appears to be the case that the comparator is supportive care and the intervention is metreleptin plus a reduced amount of supportive care, where supportive care is lipid-lowering and anti-hyperglycaemic therapies. It also appears to be the case that lifestyle modifications include both diet and exercise and that these, by their omission from further explanation or costing in the economic model, are implicitly assumed to be common to both intervention and comparator. This assumption is questionable in that there is potential for variation both in clinical practice and between sources of evidence for intervention and comparator.

3.3.4 Outcomes

The outcomes listed are consistent with the scope, including the re-interpretation by the company, which seems reasonable. From the main trials, the NIH studies 991265/20010769, full summary statistics (mean and SD) were reported in the CS for the co-primary endpoints of HbA1c, triglycerides. They were also reported for secondary endpoints including ALT and AST. Results for other outcomes i.e. liver volume and food intake were reported, but selectively from the NIH studies 991265/20010769, with references to other publications by Safar Zadeh 2013 and Moran 2004 cited.[38, 39]

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 de novo SLR was undertaken to search for relevant clinical studies for metreleptin and comparators. The literature review updated the review from the previous submission but employed a new search strategy. Combined searches were performed for clinical, economic evaluations, utility, and cost and resource use studies. Table 11 of the CS details how key concerns raised by the ERG regarding the searches in the previous submission were addressed in this submission. Search strategies were reported in detail in Appendix 1 (section 17.1). The search was conducted on 16 October 2019. The selection of databases searched was adequate (Medline, Medline in Process, EMBASE, and the Cochrane Library Databases), all database searches were reported and for the most part were reproducible. A summary of the resources search is detailed in Table 4.1.

Table 4.1 Data sources for the clinical effectiveness systematic review (as reported in CS)

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Embase	Embase.com	October 2009 to October 2019	16 October 2019
	MEDLINE and MEDLINE In-Process	Embase.com	October 2009 to October 2019	16 October 2019
	Cochrane Central Register of Controlled Trials	Cochrane Library	February 2017 to October 2019	16 October 2019
Conference proceedings	European Association for the Study of Diabetes (EASD)	Not reported	2018-2019	16 October 2019
	European Conference of Endocrinology (ECE)			
	European Society for Paediatric Endocrinology (ESPE)			
	Paediatric Endocrine Society (PES)			
Websites	FDA	Not reported	Not reported	16 October 2019
	EMA			
	Google Scholar			
Clinical trial registries	US NIH registry & results database	https://clinicaltrials.gov	Not reported	16 October 2019

ERG comment:

- The search strategies were well constructed with condition, intervention and comparator facets and contained a combination of subject heading index and free text terms, and ERG concerns

from the previous submission were addressed with the addition of comparators, more sensitive terms for the condition and fully referenced study design filters.

- Study design filters were appropriately used and based on terms designed by the Scottish Intercollegiate Guidelines Network (SIGN).
- The Cochrane library strategy contained errors in syntax and construction, however it is unlikely any relevant studies would have been missed from this source that would not have been retrieved in the other database searches (more details of the errors are provided in Appendix 1).
- Reporting of the grey literature searches could have benefited from the addition of more details to make the searches more transparent and reproducible.

4.1.2 Inclusion criteria

The eligibility criteria for the review are described in Table 4.2.

ERG comment: The eligibility criteria seem to be adequate to retrieve studies to match the NICE scope.

Table 4.2 Eligibility criteria

Inclusion criteria	
Population	Adults or children above the age of 2 with generalised lipodystrophy Adults or children above the age of 12 with partial lipodystrophy (reported to be '…limited to patients for whom standard therapy was not able to provide an adequate metabolic control.'
Interventions/comparators	Metreleptin Lifestyle modification: Diet Exercise Cosmetic surgery Hyperphagia treatment: Anorexigenic agents Appetite suppressants Bariatric surgery Anti-hyperglycaemic therapy: Insulin Thiazolidinediones Metformin DPP-4 inhibitor GLP-1 agonist SGLT-2 inhibitor Sulfonylureas HTG therapy: Statins Fibrates Fish oil Thiazolidinediones Therapeutic plasma exchange Fatty liver disease therapy:

Inclusion criteria	
	Cholic acid Any other interventional therapy for lipodystrophy
Outcomes	Triglycerides HbA1c Pancreatitis Organ damage Liver function including cirrhosis Hyperphagia Mortality Adverse events Pubertal status
Study design	Randomised controlled trials Non-randomised controlled trials Observational studies Natural history studies
Language restrictions	None
Exclusion criteria	
Population	Studies that do not include patients of interest to the SLR
Interventions/comparators	No intervention/comparators of interest
Outcomes	No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes
Study design	Individual case study reports Reviews Letters Comment articles
Language restrictions	NA
Source: Table 60, CS Abbreviations: SRL, systematic literature review	

4.1.3 Critique of data extraction

The CS states that data extraction was performed by one reviewer and the data extraction table was then checked by a second analyst.

ERG comment: This does seem to overlook the possibility of discrepancies and does not provide any method for their resolution, which would be expected according to standard practice.[40] There is therefore greater uncertainty than would be needed if standard practice had been reported to have been followed.

4.1.4 Quality assessment

Each of the included studies, NIH studies 991265/20010769 and FHA101, was critically appraised using the Downs and Black checklist, as shown in Tables 87 and 88 in Appendix 8.[1]

4.1.5 Evidence synthesis

Given the lack of head-to-head trials comparing metreleptin with or without supportive care to supportive care alone and the lack of comparative studies with a common comparator, an indirect treatment comparison (ITC) was performed based on the methods to analyse individual patient-level data (IPLD) from non-comparative studies in order to estimate a treatment effect i.e. effectiveness of one treatment vs. another, as described in NICE DSU TSD 17.[41] The methods are reported in Section 9.8 of the CS.[1]

Two single arm studies were chosen: the NIH 991265/20010769 study and GL/PL Natural History study. The basis of this choice was that the former was the 'pivotal metreleptin study' and the latter was the 'key relevant study' (p.129 and 130, CS).[1] The company also argued that the availability of IPLD from the NIH 991265/20010769 study and the GL/PL Natural History study supported the use of methods as IPW rather than relying on aggregate comparator data selecting on observables to minimise bias in order to estimate an average treatment effect (ATE) of metreleptin with or without supportive care to supportive care alone through the ITC.

Section 9.8 of the CS also contained information on the GL/PL Natural History study; this has been described in Section 4.2, with baseline characteristics in Section 4.2.1 and results in Section 4.2.4.[1]

The company justified the need for adjustment on the basis of differences in population between the two studies i.e.: 'Patients in the GL/PL Natural History study were generally less severe than patients in the NIH follow-up study. For instance, HbA1c was elevated (≥6.5%) in 74% of GL patients and 71% of PL patients in the NIH follow-up study compared with 43% of GL patients and 53% of PL patients in the GL/PL Natural History study.[1] Therefore, forming conclusions on the relative efficacy of metreleptin with or without supportive care compared to supportive care alone through a naïve comparison of the NIH follow-up study and the GL/PL Natural History study would be unreliable.' (p.130)[1]

4.1.5.1 ITC methods

The outcomes chosen for the ITC were change from baseline in HbA1c, triglycerides and liver enzyme (ALT and AST) levels, and incidence of acute pancreatitis and all-cause mortality. The company stated that the decision to include these outcomes was because these '… were the only outcomes consistently captured and reported in the NIH Follow-up study and the GL/PL Natural History study.' (p.133).[1] These outcomes were further deemed appropriate through clinical engagement.

4.1.5.2 Choice of method of adjustment

The company presented the rationale for the choice of adjustment method based on the NICE DSU TSD 17 algorithm.[41] They chose a method of selection on observables, which relies on the assumption that 'no unobserved confounding' is reasonable, the grounds for which were stated to be 'clinical validation' (p.133), although no further details were reported.[1] The method of selection of observables can then be implemented in a way that depends on the degree of overlap in characteristics likely to be correlated with the treatment effect. This was demonstrated in Figure 21 of the CS, only for age, which was the only continuous covariate that the company included in their analyses. For the categorical covariates, gender and lipodystrophy type, data were not presented. On the basis that sufficient overlap had been demonstrated, two potential methods were identified according to the NICE DSU TSD 17 algorithm, i.e. RA or IPW, although a combination of the two (doubly robust method) and matching are also options.[41] However, the latter was not deemed feasible given the relatively small sample size. The company stated that they had performed tests of suitability of 'a regression-based methodology

(multivariate regression)' (p.135), which showed that '…the model was not a good approximation of the covariates on the outcome of interest…' (p.135) and contrasted this method with RA.[1] Although it was unclear what they meant by 'multivariate regression' as opposed to RA, given that treatment was included in the multivariate regression model, it is probably what is referred to as 'regression analysis' in TSD 17, i.e. one regression model for all data regardless of treatment as opposed to separate models for each set of the GL/PL natural and NIH follow-up datasets.[41]

The test of suitability of the so-called 'multivariate regression' as opposed to IPW was a test of normality of distribution for each of the outcomes presented in Section 17.12.2, Appendix 12.[1] The company concluded that there was a violation of normality according to the Shapiro-Wilk test, visually confirmed by histogram. On this basis the company chose IPW, arguing that RA and doubly robust methodology did not need to be explored because they had compared two different methods.

ERG comment: The ERG agrees with the general methodological approach given the lack of comparative studies. Based on the answer to the clarification question A22, it also makes sense to have included only the NIH follow-up and the GL/PL Natural History studies, despite there being a number of studies deemed not to be relevant by the company, even though they met the inclusion criteria for the SLR (see Section 4.2.1), given that these two studies were the largest for which the company had access to the individual patient data.[37] The company was asked in clarification question A22 whether other indirect comparison methods could have been considered including more studies from the SLR. The company answered that after consideration, the availability of IPLD from both the aforementioned studies could allow the use of the IPW 'deemed to be superior to an analysis relying on aggregate comparator data: IPW provides a means to adjust for differences in baseline population characteristics when generating clinical effectiveness estimates.' In addition, the company conducted a further sensitivity analysis using IPW+RA, i.e. a doubly robust method, as recommended in TSD 17.[37, 41] The results of these analyses have been added to the tables in Section 4.4. The company did not perform them for mortality, 'as the model resulted in problems with convergence and overfitting, and therefore could not produce reliable treatment effect estimates.' (p.27).[37]

Given the lack of normality in the distribution of continuous variables, the ERG requested in clarification question A40 for an assessment after transformation for which the company provided the distribution of the outcome variables after transformation, which showed that the outcomes were still skewed.[37]

4.1.5.3 Missingness and imputation

Missing pancreatitis data from GL/PL study were imputed on the basis of missingness between 5% and 40% in both studies, although the reference to support this referred to randomised trial data and imputation is not mentioned in TSD 17.[41, 42] Mortality data were considered 'complete', according to the following: 'Where survival status was unknown at the outcome timepoint, individuals in both studies were censored and presumed to be alive at their last visit date.' (p.137)[1]

ERG comment: The data to support missingness between 5% and 40% i.e. Table 26 in the CS did not confirm the assertion of missingness between 5% and 40% as it appeared to show no missing pancreatitis data in the NIH follow-up study and data for 84.64% of patients in the GL/PL study.[1] In addition, the response to clarification question A29 appeared to support the results in Table 26.[37] The ERG therefore continue to be perplexed as to how the rule to apply imputation was applied.

The company was asked to clarify the basis of the mortality data completeness (question A33), and it appears that it was unknown if patients were alive at the 'last visit date'.[37] An assumption was made

that as survival status was later unknown, patients were alive at the point of the last appointment. It is unclear why patients with unknown status were not simply censored for survival analysis.

The company's response to the clarification question A37 if a check had been made regarding the assumption that missing data are missing at random (MAR), was that it was not formally verified.[37]

4.1.5.4 Baseline and outcome definition

In the NIH Follow-up study, baseline measurements of HbA1c and triglycerides were taken at metreleptin initiation. Baseline measures of ALT and AST were defined as ±3 months from the date of metreleptin initiation, as liver enzyme measures were not explicitly taken at this date. Outcome measures were taken at 1 year ±6 months post metreleptin initiation.

In the GL/PL Natural History study, baseline was defined as ±3 months from the date of diagnosis. Outcome was defined as 1 year ±6 months after the date of diagnosis. Several time point definitions were considered for the outcome measure due to the level of missing data, as both the baseline and outcome measure are required to calculate the change. Ultimately, a 1 year ±6-month time point was chosen in order to maximise the number of individuals with data available whilst remaining as consistent as possible to NIH Follow-up outcome time point.

Pancreatitis was treated as a binary outcome with any event throughout the entire study period being counted.

All deaths during the entire study period were used to estimate a hazard ratio.

ERG comment: The ERG requested clarification, in question A20, as to the discrepancy between the definition of the baseline period of the GL/PL Natural History study between that given above and that in the technical report, which was anytime between birth and diagnosis.[36, 43] The company confirmed that the baseline had been redefined for the ITC.[37]

4.1.5.5 Statistical methodology

IPW was used to estimate the average treatment effect (ATE), which corresponds to the difference in the weighted means, calculated using the inverse of the propensity score (PS) as weights. The PS is the probability of treatment assignment as a function of a set of observable covariates. Due to the relatively small sample size in the HbA1c outcome of the supportive care alone arm (n=21) compared to the metreleptin with or without supportive care arm (n=101), stabilised inverse probability weights were used in order to avoid excessively high weights in the supportive care arm.[1, 44]

An ATE was calculated using linear models for continuous outcomes (change from baseline to Month 12 in HbA1c, triglycerides, ALT and AST), generalised linear models for categorical outcomes (incidence of pancreatitis) and Cox proportional hazard models for time to event outcomes (all-cause mortality), using the propensity score weights as a link function. For continuous outcomes, the ATE was estimated by the mean difference between the two groups using the coefficient of treatment assignment. For binary outcomes, the ATE was estimated by the odds ratio (OR) using the exponential of the coefficient of treatment assignment. For time to event outcomes, the ATE was estimated by the hazard ratio (HR) using the exponential of the coefficient of treatment assignment.

Robust standard errors were calculated using a robust sandwich estimator to account for the fact that the IPW uses weighted data.

Two other sets of results were provided and reproduced in Section 4.4:

- Naïve analysis (direct comparing the results in the two groups without any adjustments) was also conducted, the results of which were given in Section 17.12.3 of the CS.[1]
- Analysis using multivariate regression, reported in Section 17.12.4 of the CS.[1]

All statistical analyses were performed using R version 3.6.1.

ERG comment: Given the lack of normality in the distribution of outcomes, the company was asked, in clarification question A23, to provide a comparison of medians using a non-parametric test in the naïve analysis. The results provided by the company provided new results using a Mann-Whitney/Wilcoxon rank-sum test and these have been included in Section 4.4.[37]

The company also provided the statistical methods for the naïve comparison of mortality, in response to clarification question A25.[37] R version 3.6.1 was used in order to produce a cox-proportional hazards model. The survival package was used alongside the coxph function to obtain p-values and 95% confidence intervals for the hazard ratio. The survfit function was used to assess the p-value of the difference between the hazard ratios.

4.1.5.6 Selection of covariates

The covariates chosen were gender, age at baseline and lipodystrophy type. The basis of this choice was reported to be clinical expert opinion as to their being confounding factors and statistical test of effect on treatment. Some covariates were stated to have been considered, but excluded on the basis of missing data (see Section 17.12.1, CS).[1]

ERG comment: The company were asked, in clarification question A23, if country was explored as a covariate, to which the company responded that it was not and its inclusion would risk overfitting.[37]

The company was also asked, in clarification question A27, to further justify the assumption of no observed confounding, particularly given the lack of inclusion of baseline measures of outcomes such as HbA1c or triglycerides or time to diagnosis. In response, they reiterated the basis in clinical expert opinion and stated that '…a sensitivity analysis using additional co-variates (history of baseline elevated HbA1c and elevated triglycerides, baseline leptin levels and baseline pancreatitis) was explored, this analysis was not feasible due to overfitting (see Section 9.8.1 in company submission).' (p.33).[37] However, the results of this analysis were not provided. The company also argued that these factors were not confounding in that they were not related to treatment allocation. However, the ignorability assumption, fundamental for the validity of the propensity score, states that one has measured and has access to all the variables that affect treatment selection and outcomes. The company also argued, in response to clarification question A35, that a sensitivity analysis including ethnicity was not feasible due to the small size of the studies.[37]

4.1.5.7 Covariate balance

As the aim of IPW method is to balance the two treatment groups regarding observed baseline covariate, this was examined through using descriptive statistics of relevant baseline of characteristics, histograms and statistical tests, as presented in Section 17.12.5 of the CS.[1]

ERG comment: The company verified the positivity assumption i.e. that none of the values of the propensity score included either zero or one, which would indicate problems with overlap of the covariates.[37] The company also showed the robustness of the IPW model to variation in methods to constrain the propensity score weights by presenting an analysis for HbA1c using trimming as opposed to stabilisation, as recommended in TSD 17.[37]

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Studies included in/excluded from the submission

As reported in Section 9.2 of the CS, the systematic review conducted by the company identified 74 publications that met the eligibility criteria.[1] These included clinical study reports (CSRs) for the National Institute of Health (NIH) NIH 991265/20010769 and FHA101 studies and the technical report for the NIH follow-up study.

The details of all 74 published references are reported in Appendix 6, Tables 67 to 83. There were 38 references to 12 observational studies which evaluated metreleptin as an intervention, 35 references which did not include metreleptin as an intervention, and one randomised controlled trial (RCT) which compared cholic acid therapy with placebo. There were no references identified to studies that compared metreleptin to standard of care alone.

Only three of the 12 metreleptin studies were considered relevant i.e. the NIH 991265/20010769 studies, an extension to this study, the NIH follow-up study, and FHA101 study.[1] Although not referred to in the CS as being a relevant study, some results from the Addenbrooke's EAP, which had run for more than 10 years, were included as supporting evidence with up to 36 months follow-up.[1] Only one non-metreleptin study the GL/PL Natural History Study, was considered relevant. Reasons for exclusion from detailed analysis or inclusion in a meta-analysis of the nine metreleptin and the other non-metreleptin studies were not reported.

ERG comment: It was unclear why so many studies were not considered relevant by the company despite their appearing to fulfil the eligibility criteria. Since all of these publications were listed as meeting the inclusion criteria specified in Section 17.5.1 (CS, Table 67, pages 286 to 287), in question A10 of the clarification letter the company were asked to explain why only results from selected publications relating to NIH studies 991265/20010769, the NIH follow-up study, study FHA101 and the GL/PL Natural History study were reported.[36] The company response was to state that the NIH studies were the largest and robust studies of metreleptin.[37] They also stated that the GL/Pl Natural History Study was the only study for which individual patient data were available for the ITC.

Many of the data in terms of baseline characteristics and outcomes for both the NIH follow-up study and the GL/PL Natural History Study were not reported in the CS. Therefore, given the use of these studies for the ITC, the ERG have added data for comparison from two technical reports provide by the company.[43, 45]

Study NIH 991265/20010769

Study NIH 991265/20010769 are considered as a single study with trial number NCT00025883, given that they had similar protocols and NIH 991265 was a pilot study with eight out of nine patients having entered the long-term NIH 20010769 study. It was an open-label, single-arm, investigator-sponsored study and conducted at the NIH in the US between 2000 and 2014, with continuous enrolment and variable duration of follow-up. Both GL and PL patients were included. The primary source of evidence was reported to be the CSR; the latest CSR is based on all available data from the final analysis on all patients (N=107) over the 14-year study period. 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: these are shown in Table 12 of the CS. Details of methodology are shown in Table 4.3.

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. 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. 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. 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.

NIH follow-up study

The NIH follow-up study extended the 991265/20010769 study by undertaking a chart review to collect long-term data from 112 patients at the NIH, 105 patients having been part of the original study. The data from this study are available via unpublished sources only. No further details were reported in the CS, although this was the study that was used to make the comparison between metreleptin and supportive care in the ITC, as reported in Section 9.8 of the CS (see Section 4.4 of the ERG report).

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 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. 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. 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 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. Details or methodology are shown in Table 4.3.

Baseline characteristics: comparison between metreleptin studies i.e. NIH991265/ 20010769, FHA101 and Addenbrooke's EAP data

The NIH991265/20010769 study (Table 4.4) included a much higher proportion of participants with GL, 66/107 (62%) than the FHA101 study (Table 4.5), 9/41 (22%). The proportion of patients with GL in the Addenbrooke's EAP data was approximately 33% (Table 4.6). 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] The age distribution of patients in the Addenbrooke's EAP was similar to that of patients in the NIH 991265/20010769 study, with 71.4% of GL <18 years of age and 80% of PL patients ≥18 years of age at diagnosis. In general, the baseline metabolic measures for patients in study FHA101 were not as elevated as those for patients in study NIH 991265/20010769, but the values in the Addenbrooke's data were very similar to those in the NIH 991265/20010769 study. However, there was a large discrepancy in the PL patients with respect to the use of lipid-lowering medications with about 85% use in the NIH

991265/20010769 study vs. only 20% in the Addenbrooke's data. No baseline characteristics were provided for the NIH follow-up study in the CS.[1]

ERG comment: Whilst there is much similarity in the baseline characteristics between the NIH991265/ 20010769 study and the Addenbrooke's data, there is a large discrepancy in the use of lipid-lowering medication, at least for PL patients. This may reflect differences in clinical practice between the UK and the US and may have implications for the applicability of the NIH991265/20010769 study to UK clinical practice which is of significance to the decision problem given the use of these data (in the form of the NIH follow-up study) in the ITC and thence in the economic model (see Sections 4.4 and 5.).

GL/PL natural history study

A description of the study methodology was presented in Section 9.81 of the CS. The GL/PL Natural History study is based on an international chart review of 230 patients with GL or PL. The study observation period was defined as the time period that spanned from birth until loss to follow-up, death, or date of chart abstraction, whichever occurred first. The date when the first signs of lipodystrophy appeared (e.g. visible lipodystrophy, diagnosis of diabetes and/or insulin resistance, and elevated triglycerides or liver enzymes) was denoted as the 'first reported evidence of GL or PL'. Any time prior to the initial diagnosis of GL or PL was defined as the 'baseline period', and any time on or following this diagnosis was defined as the 'follow-up period'. The date of last available data in each medical chart, at which a patient may be lost to follow-up, deceased, or still alive and being followed at their respective treatment centres, marked the end of the observation period for all patients.

Baseline characteristics: comparison between NIH991265/20010769 and GL/PL natural history study

Some baseline characteristics for the GL/PL natural history study were reported in Table 25 of the CS (Table 4.7). However, the type of information given was generally quite different to that presented for the NIH991265/20010769 study (Table 4.4). Nevertheless, it can be seen that in the GL/PL Natural History study there were fewer females than in the NIH991265/20010769 study: 60% vs. 77% for GL patients and 75% vs. 98% for PL patients. Also, whilst the NIH 991265/20010769 study was conducted in the US, over 50% of patients in the GL/PL Natural History study were treated in either Turkey or Brazil.

Baseline characteristics: comparison between NIH follow-up study and GL/PL natural history study

Although the ITC used the NIH follow-up study as the source of metreleptin treated patient data, almost no baseline characteristics were presented in the CS.[1] The CS did report that patients in the GL/PL Natural History Study were generally less severe than patients in the NIH follow-up study, stating that HbA1c was elevated (≥6.5%) in 74% of GL patients and 71% of PL patients in the NIH follow-up study compared with 43% of GL patients and 53% of PL patients in the GL/PL Natural History study.

ERG comment: Given the importance of the comparison, the ERG have compiled a table (Table 4.8) of baseline characteristics for the NIH follow-up study, from the technical report supplied by the company, in order to facilitate a comparison with the GL/PL Natural History Study, the source of data for standard care in the ITC (Table 4.7).[45]

It can be seen that there are some issues with comparability between these two studies, such as lack of clarity in whether some laboratory values were obtained after fasting (HbA1c, leptin), differences in method of calculation of the mean (triglycerides) and threshold for determining abnormality (ALT, AST). Overall, the ERG notes that the GL/PL Natural History Study patients were less severe than the

NIH follow-up study patients, specifically in terms of the following biochemical markers: leptin, HbA1c, triglycerides, ALT and AST. This might explain the much higher use of medication at baseline, between about 80% and 90% use of anti-diabetic medication in the NIH991265/20010769 study vs. under 60% use of any kind of anti-diabetic or lipid-lowering medication in the GL/PL Natural History Study. The biggest difference between the two studies is the proportion of GL to PL patients with 35% who have GL in the GL/PL Natural History Study vs. 61% in the NIH follow-up study. Given that GL generally is perceived to have the worst prognosis, one would already expect the GL/Pl Natural History Study patients to be less severe at baseline, the observed difference in severity remains consistent within GL and PL. The question then arises as to how it is that patients recruited to the NIH991265/20010769 study had more severe disease than that observed in the GL/PL Natural History Study. The company chose only three baseline characteristics to adjust for in the ITC, based on clinical opinion, i.e. lipodystrophy type (GL or PL), gender and age at baseline (see Section 4.1.5). The ERG can confirm that there is a clear difference in percentage of GL and female patients between the two studies. However, the difference in age at baseline is less discernible, particularly given that for the ITC baseline was at diagnosis for the GL/PL Natural History Study, but it was at metreleptin initiation for the NIH follow-up study. For PL, mean baseline age was 33.7 vs. 34.6 and for GL, it was 12.3 vs. 17.5 for GL/PL natural history vs. NIH follow-up respectively.

Table 4.3 Summary of study methods, reproduced from Tables 14 and 15, CS

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 (including subgroup of PL patients with baseline leptin <12 ng/mL and HbA_{1c} ≥6.5% and/or triglycerides ≥5.65 mmol/L)[a]
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)[a]
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 4.4 Baseline characteristics for study NIH 991265/20010769, reproduced from Table 16, CS

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)	8.7 (3.6, 26.5)	8.8 (5.0, 20.4)	7.0 (2.7, 20.4)
Fasting triglycerides, mmol/L			
Median (range)	4.6 (0.6, 143.3)	5.5 (1.2, 109.5)	4.1 (1.1, 109.5)
≥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

Table 4.5 Baseline characteristics for study FHA101, reproduced from Table 17, CS

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)
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 4.6 Baseline characteristics for Addenbrooke's EAP, reproduced from Table 18, CS

Characteristic	GL (N=10)	PL (N=21)	
		PL subgroup[a] (N=18)	Overall (N=21)
Female, n (%)	7 (70.0)	16 (88.9)	19 (90.5)
Race n (%)			
Caucasian	4 (40.0)	16 (88.9)	19 (90.5)
Asian	5 (50.0)	1 (5.6)	1 (4.8)
Unknown	1 (10.0)	1 (5.6)	1 (4.8)
Age at diagnosis, median (range)[b]	1 (1, 21)	23 (1, 53)	34.5 (1, 53)
<18 years, n (%)	5 (71.4)	2 (28.6)	2 (20.0)
≥18 years, n (%)	2 (28.6)	5 (71.4)	8 (80.0)
Lipodystrophy type, n (%)			
Acquired	3 (30.0)	1 (5.6)	1 (4.8)
Congenital/Familial	7 (70.0)	17 (94.4)	20 (95.2)
BMI, kg/m^2, median (range)[b]	19.5 (13.4, 24.6)	24.9 (22.2, 28.8)	24.9 (22.2, 28.8)
HbA1c, %[b]			
Median (range)	9.1 (5.1, 13.5)	7.3 (6.2, 15.3)	7.1 (5.7, 15.3)
≥6.5, n (%)	8 (88.9)	16 (88.9)	17 (81.0)
≥8.0, n (%)	8 (88.9)	7 (38.9)	7 (33.3)
Fasting triglycerides, mmol/L[b]			
Median (range)	4.6 (1.7, 17.1)	3.4 (1.5, 26.5)	3.2 (1.1, 26.5)
≥2.26 mmol/L, n (%)	9 (90.0)	14 (82.4)	15 (75.0)
≥5.65 mmol/L, n (%)	5 (50.0)	2 (11.8)	2 (10.0)
Anti-diabetic medications at baseline, n (%)[b]	7 (70.0)	7 (100.0)	10 (100.0)
Triglyceride-lowering medications at baseline, n (%)[b]	2 (28.6)	1 (20.0)	1 (14.3)

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

Table 4.7 Baseline characteristics for the GL/PL Natural History Study, taken from Table 25, CS

Characteristic	All (N=230)	GL (N=81)	PL (N=149)
Female, n (%)	160 (69.6)	48 (59.3)	112 (75.2)
Age at first symptoms in y, mean (SD)	19.2 (16.5)	9.2 (11.9)	24.7 (16.1)
Age at initial diagnosis in y, mean (SD)			
median (IQR)[c]	26.2 (18.4)	12.3 (13.7)	33.7 (16.1)
	25 (11-41)	9 (1-18)	33 (22-47)
Age at first visit to treatment centre in y, mean (SD)	28.7 (18.2)	16.1 (13.9)	35.6 (16.6)
<18 years	91 (39.6)	59 (72.8)	32 (21.5)
Years from first symptoms to diagnosis, mean (SD)	6.9 (10.8)	3.1 (6.4)	9.0 (12.0)
Duration of follow-up period in y, mean (SD)	7.6 (7.9)	9.5 (8.1)	6.5 (7.6)
Race/ethnicity,[a] n (%)			
Caucasian/white	166 (72.2)	46 (56.8)	120 (80.5)
African descent/black	17 (7.4)	14 (17.3)	3 (2.0)
Other	21 (9.1)	16 (19.7)	5 (3.4)
Unknown	16 (7.0)	3 (3.7)	13 (8.7)
Country of residence, n (%)			
Brazil	52 (22.6)	25 (30.9)	27 (18.1)
Turkey	80 (34.8)	32 (39.5)	48 (32.2)
United States	93 (40.4)	22 (27.2)	71 (47.7)
Other[b]	5 (2.2)	2 (2.5)	3 (2.0)
Treatment centre, n (%)			
National Institutes of Health (United States)	66 (28.7)	23 (28.4)	43 (28.9)
University of Michigan (United States)	32 (13.9)	1 (1.2)	31 (20.8)
Dokuz Eylül University (Turkey)	80 (34.8)	32 (39.5)	48 (32.2)
Federal University of Ceará (Brazil)	23 (10.0)	19 (23.5)	4 (2.7)
Universidade de São Paulo (Brazil)	29 (12.6)	6 (7.4)	23 (15.4)
Type of lipodystrophy, n (%)			
AGL	7 (3.0)	7 (8.6)	—
APL	28 (12.2)	—	28 (18.8)
CGL	72 (31.3)	72 (88.9)	—
FPLD	121 (52.6)	—	121 (81.2)

Characteristic	All (N=230)	GL (N=81)	PL (N=149)
Generalised progeroid lipodystrophy	2 (0.9)	2 (2.5)	—
Leptin, ng/ml, mean (SD)[c]	9.0 (7.9)	10.1 (12.6)	8.8 (7.7)
HbA_{1c}, %[c]			
Mean (SD)	7.3 (2.3)	7.1 (3.3)	7.4 (2.0)
≥6.5, n (%)	27 (54)	4 (44.4)	23 (56.1)
Triglycerides, mg/dL[c]			
Mean (SD)	555.8 (1373.6)	401.6 (283.5)	623.5 (1636.8)
>200 mg/dL	53 (64.6)	19 (76.0)	34 (59.6)
Elevated ALT[c,d]	24 (27.6)	11 (37.9)	13 (22.4)
Elevated AST[c,d]	11 (12.9)	6 (20.7)	5 (8.9)
Baseline medication data available, n (%)[e]	89 (38.7)	30 (37.0)	59 (39.6)
Any baseline medication use, n (%)	45 (50.6)	10 (33.3)	35 (59.3)
Any fibrates, n (%)	19 (21.3)	5 (16.7)	14 (23.7)
Any statin, n (%)	8 (9.0)	1 (3.3)	7 (11.9)
Any insulin, n (%)	19 (21.3)	6 (20.0)	13 (22.0)
Any oral antidiabetic agent, n (%)	34 (38.2)	6 (20.0)	28 (47.5)

Abbreviations: AGL, acquired generalised lipodystrophy; APL, Acquired partial lipodystrophy; CGL, Congenital generalised lipodystrophy; FPLD, Familial partial lipodystrophy; GL, Generalised lipodystrophy; PL, Partial lipodystrophy; SD, Standard deviation.

[a]One patient in the United States was marked as "Caucasian" and "Other." Because of this, the sum of patient counts for the race/ethnicity categories may exceed the total number of patients.

[b]Other countries included Argentina, Bahamas, Greece, Israel, and the United Kingdom.

[c]Obtained from technical report.[43]

[d]55 U/L for ALT, 48 U/L for AST,

[e]Baseline medication data provide in response to clarification.[37]

Table 4.8 Baseline characteristics for study NIH follow-up study, reproduced from Technical report[45]

Characteristic	All (N=105 to 112)	GL (n=64 to 68)	PL (n=44)
Female, n (%)	93 (83)	51 (75)	42 (95.5)
Race, n (%)			
Caucasian	67 (63.8)	31 (48.4)	36 (87.8)
Black	16 (15.2)	16 (25)	0
Asian/Native American/Hispanic/Other	4 (3.8)/ 1 (1.0)/ 12 (11.4)/ 5 (4.8)	3 (4.7)/ 1(1.6) / 10 (15.6)/ 3 (4.7)	1 (2.4)/ 0/ 2 (4.9)/ 2 (4.9)
Age at first symptoms, years			
Mean (SD)	13.4 (11.2)	8.8 (7.1)	20.1 (12.6)
Age at metreleptin initiation, years			
median (IQR)	18 (14-35)	15 (12-20)	35 (19- 46)
mean (SD)	24.3 (15.4)	17.5 (11.4)	34.6 (15.2)
<20 years	61 (54.5)	49 (72.0)	12 (27.2)
≥20 years	51 (45.5)	19 (28.0)	32 (72.8)
LD type, n (%)			
AGL	20 (17.9)	20 (29.4)	-
APL	6 (5.4)	-	6 (13.6)
CGL	48 (42.9)	48 (70.6)	-
FPL	38 (33.9)	-	38 (86.4)
Fasting leptin, ng/ml, mean (SD)	3.3 (3.4)	1.3 (1)	6.4 (3.5)
HbA_{1c}, %			
Mean (SD)	8.4 (2.3)	8.7 (2.3)	8 (2.2)
≥6.5, n (%)	83 (74.8)	52 (77.6)	31 (70.5)
Fasting triglycerides, mg/dL			
Mean - geometric (IQR)	531.9 (228-1219)	545.2 (20-1251)	512.5 (244-841)
>200 mg/dL	89 (80.9)	52 (78.8)	37 (84.1)
Elevated ALT[a]	57 (54)	45 (70)	12 (29)
Elevated AST[a]	48 (46)	38 (59)	10 (24)
Anti-diabetic medications at baseline, n (%)	100 (89.3)	57 (83.8)	43 (97.7)
Lipid-lowering medications at baseline, n (%)	58 (51.8)	28 (41.2)	30 (68.2)

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] ALT: females, >50 U/L; males >66 U/L, AST >40 U/L

4.2.2 Details of relevant studies not included in the submission

In addition to the studies included in the systematic review, but not found to be relevant by the company, Table 3 in the CS summarised three studies that were ongoing that were deemed to be relevant to the decision problem:

- QuaLip (data on file), designed to identify a core set of outcome measures to estimate the subjective burden of LD in those who are metreleptin naïve.
- Addenbrooke's data collection (data on file), designed to follow-up patients on metreleptin post-publication of a NICE recommendation.
- ECLip LD Disease Registry, requested by the EMA, for the company to include all patients with GL or PL treated with metreleptin to evaluate the long-term safety and effectiveness of treatment with metreleptin under routine clinical practice.[46, 47]

ERG comment: The ERG notes that, although the CS includes data from the Addenbrooke's EAP, no data from the ECLiP LD disease registry have been provided.

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, the NIH study 991265/20010769 and FHA101 in Tables 87 and 88 in Appendix 8, using the Downs and Black checklist.

ERG comment: These critical appraisals were appropriately performed. 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

The following is a summary of the results presented in Section 9 of the CS, supplemented by various appendices.[1] We have also added further results for clinical outcomes, which were not included in the CS, and results from the NIH follow-up study and the GL/PL Natural History Study, for which no results were reported in the CS.

4.2.4.1 Efficacy

Change in HbA1c and triglycerides

The single arm metreleptin treatment study, NIH991265/20010769, found statistically significant reductions in both HbA1c and triglyceride levels in both GL and PL patients.[1] The mean (SD) actual change in % HbA1c, from baseline to month 12 of treatment, LOCF, was -2.2 (95% CI: -2.7, -1.6) for GL patients, -0.9 (95% CI: -1.4, -0.4) for the PL subgroup and -0.6 (95% CI: -1.0, -0.2) for all PL patients. The corresponding values, for % change in triglyceride levels, were -32.1% (95% CI: -51.0%, -13.2%) for GL patients, -37.4% (95% CI: -46.9%, -25.2%) for the PL subgroup and -20.8% (95% CI: -37.1%, -4.6%) for all PL patients. Full results for markers of glycaemic control and lipid metabolism are provided in Table 4.9 below, reproduced from the CS (CS, Table 21).[1]

The CS also includes some subgroup data for changes in percentage HbA1c and triglycerides. In general, greater mean decreases from baseline to the primary end point of Month 12/LOCF were observed amongst patients who had higher baseline percentage HbA1c 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 4.10 below, reproduced from the CS (CS, Table 22).[1]

The smaller, single arm metreleptin treatment study, FHA101, 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 4.11 below, reproduced from the CS (CS, Appendix 10).[1]

Additional data were presented in the CS (Table 23) to support the persistence of these effects to 36 months (Table 4.12).

Given that this is the only source of efficacy data for either the GL/PL Natural History Study or the NIH follow-up study reported in the CS, Table 4.13 shows the results of the naïve comparison made with supportive care using the NIH follow-up and the GL/PL Natural History data, which were presented in Appendix 12, Section 17.12.3.[1] This shows a statistically significant difference in favour of metreleptin.

ERG comment: The naïve comparison is limited by the potential lack of comparability between the NIH follow-up and GL/PL Natural History studies. It is notable that the 12 month change in HbA1c shown for the NIH follow-up study for the whole population, as reported for the naïve comparison, is similar those shown for the original NIH 991265/20010769 study, however, the change is larger than that observed in the Addenbrooke's EAP data e.g. for all patients, -1.94% HbA1c in the NIH follow-up study vs. the highest value, which is -1.5 % HbA1c, for GL patients in the Addenbrooke's EAP data.

For 12 month change in triglycerides there is a surprisingly large difference between the NIH follow-up and the NIH 991265/20010769 studies e.g. the value for the NIH follow-up study was reported to be -51.8 mmol/l for all patients (ERG correction of the conversion from the reported mg/dL value gives a value of -10.54 mmol/L) vs. the largest change reported in the NIH991265/20010769 study, which is for GL patients, from 14.7 to 4.5 mmol/l (about -10.2 mmol/l). Even following the ERG correction, the difference between the NIH follow-up study and the Addenbrooke's EAP data is large: indeed, there is a greater similarity between the Addenbrooke's EAP data and the GL/PL Natural History study results: e.g. for GL patients there is a change of -3.5 mmol/l (Addenbrooke's EAP) vs. -10.54 mmol/l (NIH follow-up) or -4.43 mmol/l (GL/PL Natural History). If the Addenbrooke's EAP patients have similar baseline characteristics to the NIH991265/20010769 study and given that they have been obtained from the UK, then serious doubt must be cast on the representativeness of the NIH follow-up study results, most of the patients of whom come from the NIH 991265/20010769 study, to the UK setting.

The ERG also had concerns regarding the quantity and handling of missing data using LOCF analysis, particularly for HbA1c. In response to clarification question 18, the company provided the numbers, which showed that there were missing data at 12 months for 21/62 GL and 9/40 PL patients.[37] The ERG noted that, in the clinical study report (CSR), another method of imputation, worst observation carried forward (WOCF) had been employed (Table 14.2.1.1.1E, CSR).[48] However, this produced the same result as LOCF for GL patients given that the WOCF imputation method only takes into account results that are at least 6 months (180 days) post-baseline and there was only one additional observation time point post-six months i.e. at eight months. For PL patients there was little difference, and this might have been explained by one patient having been excluded from the LOCF analysis (See footnote b, Table 4.9). One additional analysis undertaken was to omit those patients for whom there were missing 12-month data i.e. on the 'Evaluable Analysis Set' (EAS). This showed a small reduction from -0.6 to -0.5 in the mean change from baseline at 12 months and a widening of the 95% CI to -1.1 to -0.0 (Table

14.2.1.1.1B, CSR).[48] The same analysis for triglycerides in the PL population showed a decrease in mean percentage change from baseline to -18.8% and a widening of the 95% CI to -38.5% to 1.0%.

Table 4.9 Glycaemic control and lipid metabolism results from NIH 991265/20010769 study

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 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	-49.6, -25.2	-37.1, -4.6
Effect size: absolute change from baseline (mmol/L)	**Mean SD)**	-10.3 (22.51)	-9.66 (20.3)	-7.06 (18.0)
	95% CI	4.59, 16.02	1.94, 17.38	1.23, 12.90
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; 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

Table 4.10 Subgroup analyses of 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)

	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
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 4.11 Glycaemic control and lipid metabolism, results from FHA101 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 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
Effect size: absolute change from baseline (mmol/L)	Mean (SD)	-21.43 (38.86)	-0.43 (1.49)	-2.80 (10.36)
	95% CI	-26.82, 69.68	-0.95, 1.81	-1.38, 6.99
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; 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

Table 4.12 Glycaemic control and lipid metabolism results from Addenbrooke's EAP

Study name		NIH 991265/20010769		
Size of study groups	Treatment	GL = 10		
Study duration	Time unit	PL subgroup[a] = 18		
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		
Change from baseline in HbA1c (%)				
		GL N=10	PL subgroup N=18[a.]	PL overall N=21
Baseline value	n	9	18	21
	Mean (SD)	9.6 (2.37)	8.3 (2.34)	8.0 (2.30)
Month 12 value[b]	n	7	5	6
	Mean (SD)	8.8 (2.41)	7.2 (0.08)	7.2 (0.09)
Month 36 value[c]	n	3	4	5
	Mean (SD)	8.9 (3.05)	6.5 (0.62)	6.5 (0.54)
Effect size: actual change from baseline at Month 12[b]	n	6	5	6
	Mean (SD)	-1.5 (2.41)	-1.1 (2.04)	-0.8 (1.97)
Effect size: actual change from baseline at Month 36[c]	n	3	4	5
	Mean (SD)	-1.1 (6.88)	-1.6 (1.52)	-1.2 (1.61)
Change from baseline in triglycerides (mmol/L)				
		GL N=62	PL subgroup N=29[a, b]	PL overall N=39[b]
Baseline value	n	10	17	20
	Mean (SD)	6.4 (5.06)	4.7 (5.74)	4.2 (5.40)
Month 12 value[b]	n	7	5	6
	Mean (SD)	4.6 (4.21)	3.2 (2.18)	3.2 (1.96)

Month 36 value[c]	n	3	4	5
	Mean (SD)	4.1 (4.91)	1.8 (1.83)	1.6 (0.69)
Effect size: percent change from baseline at Month 12[b]	n	7	4	5
	Mean (SD)	-48.4 (20.30)	-30.8 (32.95)	-22.3 (34.25)
Effect size: percent change from baseline at Month 36[c]	n	3		
	Mean (SD)	-57.6 (28.02)	-19.9 (42.02)	-23.9 (35.24)

Abbreviations: GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; 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]Defined as the 4th visit (Month 12) to Addenbrooke's Hospital where the 1st visit is at baseline i.e. metreleptin initiation.

[c]Defined as any visit to Addenbrooke's Hospital between Month 30 and Month 42

Table 4.13 Glycaemic control and lipid metabolism results from naïve comparison

Intervention (study)	Mean change from baseline to month 12 (SD)	95% CI	SE	Absolute difference with metreleptin with or without supportive care versus supportive care alone (%)	95% CI, difference with metreleptin with or without supportive care versus supportive care alone	p-value
HbA1c change (%)						
Metreleptin with or without supportive care (NIH Follow-up study)	-1.94 (1.98)	-2.33; -1.55	0.20	1.66	0.90; 2.35	<0.001*
supportive care (GL/PL Natural History Study)	-0.31(1.38)	-0.94; 0.32	0.30			
Triglyceride change mg/dL, [mmol/L]						
Metreleptin with or without supportive care (NIH Follow-up study)	-932.45 (2090.42) [-10.54 (23.62)][a]	1345.12; -519.77 [74.73; -28.88]	208.00 [11.56]	852.46 [47.36]	423.30; 1281.63 [23.52; 71.20]	<0.001*
Supportive care (GL/PL Natural History Study)	-79.98 (411.67) [-4.43 (22.87)]	-202.24; 42.27 [-11.24; 2.34]	60.70 [3.38]			

Abbreviations: CI, Confidence interval; GL, Generalised lipodystrophy; NIH, National Institutes of Health; PL, Partial lipodystrophy; SD, Standard deviation; SE, Standard error

* denotes significance at the p<0.05 level

[a] conversion corrected by the ERG (original value incorrectly reported as -51.80 (116.13)

Liver function (hepatic enzymes)

Data from the NIH 991265/20010769 study,[1] suggest that metreleptin treatment may be associated reductions in hepatic enzyme levels. In the 41 GL patients with hepatic enzyme 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 4.14 below, reproduced from the CS (CS, Table 21).[1] No assessments of statistical significance were presented.

Similar results were reported for the smaller FHA101 study in Appendix 10, CS (see Table 4.15).[1]

No liver enzyme results were provided for the Addenbrooke's EAP data.[1]

Given that this is the only source of efficacy data for either the GL/PL Natural History Study or the NIH follow-up study reported in the CS, Table 4.16 shows the results of the naïve comparison made with supportive care using the NIH follow-up and the GL/PL Natural History data, which were presented in Appendix 12, Section 17.12.3.[1] This shows a statistically significant difference in favour of metreleptin.

ERG comment: The naïve comparison is limited by the potential lack of comparability between the NIH follow-up and GL/PL Natural History study, although it is also notable that the 12 month change in ALT shown for the NIH follow-up study for the whole population, as reported for the naïve comparison, lies somewhere between those shown for GL and PL patients in the original NIH 991265/20010769 study. However, for AST, the value of -29.41 U/L for combined GL/PL patients in the NIH follow-up study is higher than the highest value, which is -23.8 U/L, which is for GL patients for the NIH 991265/20010769 study. This is a challenge to explain given that the value for PL patients is -5.1 U/L.

Table 4.14 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

Table 4.15 Hepatic enzymes results from FHA101 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

Table 4.16 Liver enzyme results from naïve comparison

Intervention (study)	Mean change from baseline to month 12 (SD)	95% CI	SE	Absolute difference with metreleptin with or without supportive care versus supportive care alone (%)	95% CI, difference with metreleptin with or without supportive care versus supportive care alone	p-value
ALT change, U/L						
Metreleptin with or without supportive care (NIH Follow-up study)	-41.36 (96.94)	-60.70; -22.03	9.74	41.07	19.33; 62.81	<0.001*
supportive care (GL/PL Natural History Study)	-0.29 (32.97)	-10.57; 9.98	5.09			
AST change, U/L						
Metreleptin with or without supportive care (NIH Follow-up study)	-29.41 (62.29)	-41.84; -16.99	6.26	26.15	12.50; 39.80	<0.001*
Supportive care (GL/PL Natural History Study)	-3.27 (17.88)	-9.14; 2.61	2.90			

Abbreviations: CI, Confidence interval; GL, Generalised lipodystrophy; NIH, National Institutes of Health; PL, Partial lipodystrophy; SD, Standard deviation; SE, Standard error

* denotes significance at the p<0.05 level

Liver damage

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] 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%.

The CS stated that 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 non-alcoholic steatohepatitis (NASH) were reported in the publication by Safar-Zadeh et al.2013[39].[1]

ERG comment: Unfortunately, although some liver pathology results were presented, which suggested some improvement in liver pathology on metreleptin, the CS lacks long-term data about the effects of metreleptin on the development and progression of liver disease. However, the technical report for the NIH follow-up study was available.[45] The mean follow-up period for GL patients was 8.8 years and the mean follow-up period for PL patients was 7.7 years. It was reported that there was an improvement in liver abnormality in 38/105 (36%) of all patients, including 32/63 (51%) of GL and 6/42 (14%) of PL patients. The main issue with these figures is that liver abnormality was defined according to a change in ALT or AST, which is a surrogate outcome measure and is unlikely to be an adequate indicator of long term clinical outcomes, and therefore provides little further information than the mean changes in ALT or AST already presented.[45] Nevertheless, although some patients seemed to improve, others worsened: of the five GL patients who had no evidence of liver abnormalities before metreleptin treatment, three (60%) had emergent liver abnormalities after metreleptin initiation; both patients (100%) with no evidence before metreleptin in the PL population emergent liver abnormalities.[45] In response to the clarification letter the company provided further details for the Safar-Zadeh et al.2013 study.[39] Patients with liver fibrosis at baseline remained stable on metreleptin.[1] Results of paired liver biopsies from 27 patients showed that 86% had borderline or definite NASH at baseline and 33% had NASH after leptin replacement for 25.8 ± 3.7 months ($p = 0.0002$).[39]

The CS also lacks any comparator results for development and progression of liver disease from the GL/PL Natural History Study, but the technical report for this study was provided.[43] This report included information on the lifetime prevalence of liver damage (including cirrhosis, hepatic steatosis and hepatomegaly) i.e. 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 9.5 years and the mean follow-up period for PL patients was 6.5 years.[43] Over the whole observation period, 71/81 (87.7%) of GL patients and 96/149 (64.4%) of PL patients were found to have liver damage.[43] 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 56 GL patients who did not have liver damage at baseline 46 (82%) developed liver damage during follow-up and 67/120 (56%) of PL patients who did not have liver damage at baseline developed damage during follow-up.

Heart and kidney damage

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[45] 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.[45] 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. [45] No indication of mean/median length of follow-up was provided.

Similarly, the study report for the NIH follow-up study[45] 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, 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, 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, 11 (50%) had emergent kidney abnormalities after metreleptin initiation, and 9/19 (47%) of PL patients who had no evidence of kidney abnormalities before treatment had emergent abnormalities after metreleptin initiation.[45]

The CS did not report any comparator results for development and progression of heart or kidney damage (from the GL/PL natural history study), but the technical report for this study was provided.[43] Over the whole observation period, 46/81 (56.8%) of GL patients and 57/149 (38.3%) of PL patients were found to have kidney damage, and 29/81 (35.8%) of GL patients and 43/149 (28.9%) of PL patients were found to have heart damage.[49] 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 77 GL patients who did not have kidney damage at baseline 42 (55%) developed kidney damage during follow-up and 42/134 (31%) of PL patients who did not have kidney damage at baseline developed damage during follow-up. Using the same approach, of the 74 GL patients who did not have heart damage at baseline 22 (30%) developed heart damage during follow-up and 33/139 (24%) 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[38] 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.[38] In Section 17.9.1, Appendix 9, the CS reported that in an evaluation of eight patients treated in Study NIH 991265, metreleptin treatment significantly decreased satiation time (the time to voluntary cessation of eating from a standardised food array after a 12-hour fast), increased satiety time (the time to hunger sufficient to consume a complete meal after consumption of a standardised preload), decreased energy consumed to produce satiation, and decreased the amount of food desired in the postabsorptive state.[50]

ERG comment: The Moran 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.[38]

The study report for the NIH follow-up study states only that 'Hyperphagia was determined by NIH investigators based on patient self-report and/or physician assessment in medical charts.' (p.27*)*.[45] At baseline, 51/62 (82%) of GL patients and 23/32 (72%) of PL patients for whom such data were available were classified as having hyperphagia. Similarly, the NIH follow-up study states that 'Clinical improvement was based on self-report and/or physician assessment as recorded in the patient medical chart. Improvement was assessed by the last NIH visit.' P.29).[45] Based on this definition, all (100%) of the 51 GL patients and 22/23 (96%) of PL patients who had hyperphagia at baseline were classified as having experienced improvements in hyperphagia.[45] 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.

The CS did not report any comparator results for hyperphagia and the GL/PL natural history study did not report any information about hyperphagia.[43]

Concomitant medication use

The CS, in Section 17.9.1, Appendix 17.9, 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] 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] 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]

ERG comment: The CS did not include any data on concomitant medication use from the NIH follow-up study. The study report for the NIH follow-up study,[45] 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.[45] 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.[45] 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.[45] 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.[45] 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.[45] Most discontinuations were for bolus insulin or metformin, only two GL patients discontinued basal insulin or insulin + metformin.[45] 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 medications.[45] The majority of discontinuations, 26/35, were for fibrates, with few patients discontinuing statin use.[45]

Growth and development

The CS included some information, from the NIH 991265/20010769 study, about growth and development in metreleptin treated patients.[1] 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]

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]

ERG comment: The NIH follow-up study[45] did not report any additional information about the growth and development of metreleptin-treated patients. The GL/PL Natural History Study[43] does not include any information about growth and development.

Reproductive dysfunction

The clinical effectiveness section of the CS did not include any evidence about the effects of metreleptin treatment on reproductive dysfunction.[1]

ERG comment: The NIH follow-up study[45] reported 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 were 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.[45] 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').[45] Clinical improvement was defined as '…more regular menstruation or decreased signs/symptoms of PCOS) by the last NIH visit date based on patient chart notes.' (p.28).[45] In contrast, three (50%) of the six previously unaffected GL patients and four (80%) of the five previously unaffected PL patients were reported as having post-metreleptin newly emergent disruption to reproductive function.[45]

The CS did not report any comparator results for reproductive dysfunction (from the GL/PL natural history study). However, the report of the GL/PL natural history study 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. Over the whole observation period, 16/48 (33.3%) of female GL patients and 40/112 (35.7%) of female PL patients were found to have reproductive dysfunction.[49] 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 32 female GL patients who did not have reproductive dysfunction at baseline, 12 (37.5%) developed reproductive dysfunction during follow-up and 24/72 (33.3%) of female PL patients who did not have reproductive dysfunction at baseline developed problems during follow-up.

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 and the CS states 'No HRQoL data were collected in the pivotal clinical trials led by NIH identified in Section 9.' (p.153)[1]

ERG comment: The NIH follow-up study[45] 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.[45] Thirty-eight (68%) of the 56 effected GL patients and 14 (47%) of the 30 affected PL patients were reported as having post-metreleptin improvement ('improvement in any of acanthosis nigricans, hyperkeratosis, or hirsutism').[45] 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.[45] 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.[45]

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).[43] 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 19 (54.3%) of the 35 GL patients and 29 (49.2%) of the 59 PL patients in the GL/PL natural history study, for whom information was available.[49] The GL/PL Natural History Study did not include any information about the ability of LD patients to perform activities of daily living.

Survival

Survival or mortality data were not reported as part of the clinical evidence in the CS except as deaths in the safety analysis of the NIH 991265/20010769 and FHA101 studies (see Deaths section below) and as part of the ITC (See Section 4.4).[1] Those data reported for the naïve ITC in Table 99 of Section 17.12.3, Appendix 12 are reproduced in Section 4.4.

4.2.4.2 Adverse events associated with metreleptin

Study NIH 991265/20010769

A summary of treatment-emergent adverse events (TEAEs) is shown in Table 4.17, below (reproduced from the CS, Table 24).[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.[1] 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 one 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.[1]

Overall, 23 (35%) of the 66 GL patients and 7 (23%) of the 31 patients in the PL subgroup experienced a treatment-emergent SAE.[1] 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.[1]

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.[1] 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 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%).[1]

Table 4.17 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)

	GL (N=66)	PL subgroup[a] (N=31)	PL overall (N=41)
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] 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]

The CS states that in general, the safety profile in the PL subgroup was consistent with that observed in the 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 91 of Appendix 10, CS and replicated in Table 4.18, 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.[51] 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.[51] 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.[51] 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).[51]

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.[51] 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%).

Table 4.18 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)

	GL (N=9)	PL subgroup[a] (N=7)	PL overall (N=32)
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)
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, 52] 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, 52]

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 52 paediatric subjects (four in the PL subgroup and 48 with GL) enrolled and exposed to metreleptin. It also states that limited clinical data exists in children less than two years old for GL and less than 12 years old for PL patients.[1]

The CS reports that the overall, the safety and tolerability of metreleptin are similar in children and adults, as reported in the SmPC.[1, 46] In GL patients, the overall incidence of drug related adverse reactions was similar regardless of age. SAEs were reported in two paediatric patients, worsening hypertension and anaplastic large cell lymphoma. In PL patients, assessment across age groups was

limited, due to the small sample size. No adverse reactions were reported in paediatric patients in the subgroup of PL patients.

The CS includes additional information concerning 'selected adverse reactions' (CS, section 9.7.2.3, pages 126-128), for which it also cites the SmPC.[1, 46]

Pancreatitis

Across the 148 patients included in LD studies, six (4%) patients (four with GL and two with PL), experienced treatment emergent pancreatitis.[1] All patients had a history of pancreatitis and hypertriglyceridemia.[1] One of the patients who developed septic shock concurrent with pancreatitis died; the other five patients recovered and continued on treatment.[1] 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]

ERG comment: The NIH follow-up study[45] 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.[45] At baseline, 21/63 (31%) of GL patients and 23/44 (52%) of PL patients had a history of pancreatitis.[45] 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.[45] Based on these criteria, 20/21 (95%) of affected GL patients and all (100%) affected PL patients experienced improvements in pancreatitis on metreleptin treatment. In contrast, there were no (0%) newly emergent incidents in GL patients and 1/21 (5%) of previously unaffected PL patients experienced pancreatitis on metreleptin treatment.

The CS did not report any comparator results for pancreatitis from the GL/PL Natural History Study.[1] Based on the technical report, over the whole observation period (including baseline and follow-up), 8/81 (9.9%) of GL patients and 22/149 (14.8%) of PL patients experienced at least one episode of pancreatitis. [43] This report also included information on the number of patients with pancreatic 'abnormalities' during the baseline period. However, it is unclear what this means given that pancreatitis is an acute event.

The CS describes abrupt interruption and/or non-compliance with metreleptin dosing as suspected to have contributed to the occurrence of pancreatitis in several patients. Table 19 and Table 20 of the CS describe the number of premature discontinuations in study NIH 991265/20010769 and study FHA101 respectively.[1] In Table 19, 23/66 (34.8%) GL patients; 15/41 (36.6%) PL patients and 11/31 (35.5%) PL subgroup patients prematurely discontinued. In Table 20, 4/9 (44.4%) GL patients; 20/32 (62.5%) PL patients and 2/7 (28.6%) PL subgroup patients prematurely discontinued. The ERG considers that the numbers of patients who discontinue treatment are high given that discontinuation of treatment appears to be associated with an increased risk of pancreatitis.

Further evidence on pancreatitis is presented in Section 4.4 where rates were compared in the ITC.

Serious infections

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.[1]. 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.[1, 46]

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.[53] Mancuso 2002 is a study of leptin-deficient mice and should not be cited as evidence of increased infection rates in humans.[53] Moon 2013 is also cited in support of patients with LD and low leptin levels experiencing higher rates of infection than the general population.[54] Moon 2013 describes leptin's Role in lipodystrophic and non-lipodystrophic Insulin-Resistant and Diabetic Individuals and does not contain any direct evidence in support of this claim.[54]

Hypoglycaemia

Metreleptin may decrease insulin resistance in diabetic patients, resulting in hypoglycaemia in patients with LD and co-existing diabetes. [1, 46] Hypoglycaemia, deemed to be 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, 46] Generally the majority of events could be managed by food intake with only relatively few modifications of anti-diabetic medicine dosage occurring.[1, 46]

T cell lymphoma

Three cases of T cell lymphoma have been reported while taking metreleptin in clinical studies.[1, 46]All three patients had acquired GL. Two of these patients were diagnosed with peripheral T cell lymphoma while receiving metreleptin. 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 metreleptin who did not have haematological abnormalities before treatment.[1, 46]

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 tumour-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.'[55]

Immunogenicity (neutralising antibodies)

In clinical trials (studies NIH 991265/20010769 and FHA101), the rates of antidrug antibodies (ADAs) in GL and PL patients with data available were 88% (65 out of 74 patients).[1, 46]

Overall, in patients where antibody data were 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.[46]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.[1, 46]

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.'[55]

Injection site reactions

Injection site reactions were reported in 3.5% of patients with LD treated with metreleptin.[1, 46]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 metreleptin

treatment. 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),[55] 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.'

4.2.4.3 Deaths

Study NIH 991265/20010769

A summary of treatment emergent deaths was shown in Table 24 of the CS and is replicated in Table 4.19, 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.[52] 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.[52]

Table 4.19 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 91 of Appendix 10, CS and is replicated in Table 4.20, 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).[51] 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).[51]

Table 4.20 On-study deaths, study FHA101 (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

ERG comment: Deaths in the NIH follow-up study or the GL/PL natural history study were not reported in the CS, although a comparison of mortality rate was made in the ITC (see Section 4.4).[1] Therefore, the ERG have reproduced the data from the technical reports for these studies in Tables 4.21 and 4.22.

The most striking observation is the much higher median survival in terms of years from first GL/PL symptoms to death for the GL/PL natural history compared to the NIH follow-up patients, which amounts to about 15 or 30 extra years for GL or PL respectively. The effect of metreleptin to mitigate any difference due to baseline prognostic factors is very difficult to estimate, although further evidence on the company's attempt to do this is presented as part of the ITC in Section 4.4.

Table 4.21 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)

	All Patients (n=112)	GL Patients (n=68)	PL Patients (n=44)
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 4.22 Mortality and cause of death data from the GL/PL Natural History Study

	All Patients (n=230)	GL Patients (n=81)	PL Patients (n=149)
Years from first GL/PL symptoms to end of observation period*			
Mean (SD)	14.5 (12.5)	12.6 (9.5)	15.5 (13.7)
Median (IQR)	11.1 (4.8, 20.3)	10.7 (5.5, 17.0)	11.6 (4.8, 21.7)
Years from first GL/PL symptoms to diagnosis			
Mean (SD)	6.9 (10.8)	3.1 (6.4)	9.0 (12.0)
Median (IQR)	1.4 (0.0, 10.0)	0.3 (0.0, 1.6)	4.0 (0.0, 14.3)
Patients still alive, n (%)			
Yes	180 (78.3)	54 (66.7)	126 (84.6)
No	18 (7.8)	10 (12.3)	8 (5.4)
Unknown	32 (13.9)	17 (21.0)	15 (10.1)
Years from first GL/PL symptoms to death**			
Kaplan-Meier Mean (SE)	47.6 (2.0)	29.4 (1.5)	51.6 (1.9)
Median (IQR)	56.3 (34.5, NR)	31.7 (26.4, NR)	56.3 (56.3, NR)
Patients who died, n	18	10	8

	All Patients (n=230)	GL Patients (n=81)	PL Patients (n=149)
Age at first GL/PL symptoms			
Mean (SD)	22.1 (20.3)	13.5 (19.5)	32.9 (16.6)
Median (IQR)	16.9 (4.0, 30.6)	5.3 (0.3, 15.0)	29.6 (22.4, 43.0)
Age at death			
Mean (SD)	42.3 (18.4)	33.8 (17.0)	52.9 (14.7)
Median (IQR)	37.4 (30.4, 60.2)	30.9 (18.7, 44.5)	56.5 (37.4, 66.0)
Death related to lipodystrophy, n (%)			
Yes	11 (61.1)	8 (80.0)	3 (37.5)
No	0	0	0
Unknown	7 (38.9)	2 (20.0)	5 (62.5)
Patients who died, n	18	10	8
Cause of death reported,[$] n (%)	14 (77.8)	10 (100.0)	4 (50.0)
Method of assessing cause of death, n (%)			
Per practice health records	5 (27.8)	2 (20.0)	3 (37.5)
Per physician recollection	5 (27.8)	4 (40.0)	1 (12.5)
From death certificate	4 (22.2)	3 (30.0)	1 (12.5)
Not confirmed	0	0	0
Unknown	4 (22.2)	1 (10.0)	3 (37.5)
Potential contributing factors, n (%)			
Bone marrow/hematologic abnormalities	1 (5.6)	2 (20.0)	0
Cancer	0	4 (40.0)	0
Cardiovascular event	6 (33.3)	3 (30.0)	3 (37.5)
Cerebrovascular disease	3 (16.7)	1 (10.0)	2 (25.0)
Immunosuppression	1 (5.6)	1 (10.0)	0
Infection (viral)	0	0	0
Infection (bacterial)	3 (16.7)	3 (30.0)	0
Liver disease	4 (22.2)	3 (30.0)	1 (12.5)
Pancreatitis	2 (11.1)	2 (20.0)	0
Pneumonia	2 (11.1)	2 (20.0)	0
Renal failure	2 (11.1)	1 (10.0)	1 (12.5)
Sepsis	1 (5.6)	1 (10.0)	0
Unknown	5 (27.8)	1 (10.0)	4 (50.0)
Other[$$]	1 (5.6)	1 (10.0)	0
Location where patient died, n (%)			
At home	1 (5.6)	1 (10.0)	0
At the hospital	11 (61.1)	7 (70.0)	4 (50.0)
Unknown	5 (27.8)	1 (10.0)	4 (50.0)
Other[$$$]	1 (5.6)	1 (10.0)	0
*The end of the observation was defined as the earliest of: date of chart abstraction; death; loss to follow-up			

	All Patients (n=230)	GL Patients (n=81)	PL Patients (n=149)
**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, polycythaemia, acanthosis nigricans, hypertriglyceridemia), myocardial infarction, possible cardiac episode, probable end stage liver disease, and stroke $$Other potential contributing factors of death included mentions of pancytopenia, steatohepatitis, and chronic renal insufficiency $$$ Other locations where a patient died included a hotel			

4.3 Summary of evidence presented in other submissions

The ERG reviewed the non-company submissions for any evidence additional to that included in or with the CS.[56-59] Two studies cited by the National Severe Insulin Resistance (NSIR) Service at Addenbrooke's Hospital have been briefly summarised.[58] One study was cited regarding the potential long-term benefit of metreleptin on eating/satiety.[60] This prospective study of five female lipodystrophy patients with indication for metreleptin had measurements at baseline and at >150 weeks of metreleptin treatment. Behavioural aspects of hunger and satiety regulation were assessed by validated eating behaviour questionnaires and visual analogue scales assessing hunger and satiety feelings before and after a standardized meal. Hunger rated on visual analogue scales at 120 min after the meal significantly decreased from 46 ± 10 mm at baseline to 17 ± 6 mm at long-term assessment. Satiety at 5 and 120 min after the meal significantly increased from baseline to long-term assessment (5 min: 70 ± 7 mm to 87 ± 3 mm; 120 min: 43 ± 10 mm to 79 ± 8 mm). On the Three Factor Eating Questionnaire, the mean value of factor 3 (hunger) significantly decreased from 9.2 ± 0.2 at baseline to 2.6 ± 1.5 at long-term assessment. In the Inventory of Eating Behaviour and Weight Problems Questionnaire, mean values for scale 2 (strength and triggering of desire to eat) and scale 7 (cognitive restraint of eating) significantly decreased from baseline (31.6 ± 4.8 and 11.4 ± 2.2, respectively) to long-term assessment (14.0 ± 2.1 and 10.0 ± 1.9).

Another study was cited in support of the independence of diet and metreleptin effectiveness on glucose and lipid metabolism.[61] Patients with lipodystrophy were hospitalised for 19 days, with food intake held constant by a controlled diet. In a non-randomised, crossover design, patients previously treated with metreleptin (n=8) were continued on metreleptin for five days and then taken off metreleptin for the next 14 days (withdrawal cohort). This order was reversed in metreleptin-naive patients (n=14), who were re-evaluated after six months of metreleptin treatment on an ad libitum diet (initiation cohort). With food intake constant, peripheral insulin sensitivity decreased by 41% after stopping metreleptin for 14 days (withdrawal cohort) and increased by 32% after treatment with metreleptin for 14 days (initiation cohort). In the initiation cohort only, metreleptin decreased fasting glucose by 11% and triglycerides by 41% and increased hepatic insulin sensitivity. Liver fat decreased from 21.8% to 18.7%.

ERG comment: There is also some evidence of an effect of metreleptin, independent of diet, on glucose and lipid metabolism. However, given that this was not been demonstrated beyond 19 days, together with evidence that long-term metreleptin treatment (>150 weeks) has sustained effects on eating behaviour with increased satiety, as well as reduced hunger and hunger-related measures, it seems likely that any longer term effect, if it exists, would be mediated through change in diet.

4.4 Results of the ITC

Tables 4.23 to 4.28 show the results of the ITC according to each of the methods reported in the CS, those for the IPW method, naïve comparison and multivariate regression coming from Sections 9.8.1.1.5, 17.12.3 and 17.12.4 respectively. The survival curves for mortality were reproduced from the company response to clarification question A34.[37]

The difference the adjustment made varied between outcomes, the treatment effect essentially favouring metreleptin in the naïve analyses continuing to favour metreleptin for all continuous outcomes regardless of the method of adjustment. For pancreatitis the treatment effect favouring metreleptin remained statistically significant, but decreased with the IPW method and a similar results was found when using another method of adjustment, IPW + RA, provided in response to clarification.[37] For all-cause mortality, the treatment effect favouring supportive care decreased relative to the naïve comparison, but with a rise in uncertainty, as reflected by a larger p value.

Table 4.23 Mean change in HbA1c at 12 months, metreleptin w/wo supportive care vs. supportive care

Type of analysis	**ATE HbA1c (%)**	**Robust standard error (%)**	**95% CI**	**p-value**
IPW	-1.52	0.38	-2.28 to -0.77	**<0.001***
Naïve comparison (parametric analysis)	-1.66	NA	-0.90 to -2.35	<0.001*
Naïve comparison[a] (non-parametric analysis)	-1.6 (difference in medians)	NA	NR	<0.001*
Multivariate regression	-0.89	0.47	NR	**0.06**
IPW+RA[a]	-2.42	0.27	-2.95 to -1.88	**<0.001***

Abbreviations: ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; w / wo, With or without; RA, regression adjustment.
*denotes significance at the p<0.05 level
[a]Provided in response to clarification.[37]

Table 4.24 Mean change in triglycerides at 12 months, metreleptin w/wo supportive care vs. supportive care

Type of analysis	**ATE Triglycerides (mg/dL [mmol/L])**	**Robust standard error (%)**	**95% CI**	**p-value**
IPW	-915.30 [-10.34]	225.95 [2.55]	-1358.15 to -472.44 [-15.35 to -5.34]	<0.001*
Naïve comparison (parametric analysis)	-852.46 [-47.36]	NA	-423.30 to -1281.63 [-23.52 to -71.20]	**<0.001***
Naïve comparison[a] (non-parametric analysis)	-162.5 (difference in medians)	NA	NR	**<0.001***
Multivariate regression	-699.07 [-38.84]	335.58 [18.64]	NR	**0.039***
IPW+RA[a]	-902.71 [-10.20]	222.57 [2.51]	-1338.94 to -466.50 [-15.13 to -5.27]	<0.001*

Abbreviations: ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; w / wo, With or without; RA, regression adjustment.
*denotes significance at the p<0.05 level
[a]Provided in response to clarification.[37]

Table 4.25 Mean change in ALT at 12 months, metreleptin w/wo supportive care vs. supportive care

Type of analysis	**ATE ALT (U/L)**	**Robust standard error (%)**	**95% CI**	**p-value**
IPW	-44.13	11.06	-65.81 to -22.46	<0.001*
Naïve comparison (parametric analysis)	-41.07	NA	-19.33 to -62.81	<0.001*
Naïve comparison[a] (non-parametric analysis)	-16.0 (difference in medians)	NA	NR	<0.001*
Multivariate regression	-33.41	15.74	NR	**0.036***
IPW+RA[a]	-43.61	10.67	-64.52 to -22.70	<0.001*

Abbreviations: ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; w / wo, With or without; RA, regression adjustment.
*denotes significance at the p<0.05 level
[a]Provided in response to clarification.[37]

Table 4.26 Mean change in AST at 12 months, metreleptin w/wo supportive care vs. supportive care

Type of analysis	**ATE AST (U/L)**	**Robust standard error (%)**	**95% CI**	**p-value**
IPW	-27.79	6.93	-41.38 to -14.20	<0.001*
Naïve comparison (parametric analysis)	-26.15	NA	-12.50 to -39.80	<0.001*
Naïve comparison[a] (non-parametric analysis)	-8.5 (difference in medians)	NA	NR	0.008*
Multivariate regression	-20.86	10.59	NR	**0.051**
IPW+RA[a]	-27.18	6.71	-40.33 to -14.02	<0.001*

Abbreviations: ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; w / wo, With or without; RA, regression adjustment.
*denotes significance at the p<0.05 level
[a]Provided in response to clarification.[37]

Table 4.27 Incidence of pancreatitis, metreleptin w/wo supportive care vs. supportive care

Type of analysis	**Odds ratio**	**Robust standard error (%)**	**95% CI (%)**	**p-value**
IPW wo imputation	0.94	0.026	0.89 to 0.98	0.01*
IPS, w imputation	0.93	0.026	0.88 to 0.98	**0.004***
Naïve comparison	0.20 (calculated by ERG)	NA	0.05 to 0.89 (calculated by ERG)	0.037*
Multivariate regression wo imputation	0.189	0.770	NR	**0.031***
Multivariate regression w imputation	0.17	0.76	0.095	**0.019***
IPW+RA[a] wo imputation	0.93 (-0.067)	0.025	0.89 to 0.98	**0.008***
IPW+RA[a] w imputation	0.93 (-0.075)	0.026	0.88 to 0.98	**0.004***

Abbreviations: ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; w / wo, With or without; RA, regression adjustment.
*denotes significance at the p<0.05 level
[a]Provided in response to clarification.[37]

Table 4.28 All-cause mortality, metreleptin w/wo supportive care vs. supportive care

Type of analysis	**Hazard ratio**	**Robust standard error (%)**	**95% CI**	**p-value**
IPW	1.38	0.40	0.88 to 20.37 lower limit corrected by ERG)	0.42
Naïve comparison	2.05	NA	NR	0.065
Multivariate regression	1.30	0.37	NR	**0.48**
Abbreviations: CI, Confidence interval; SC, Supportive care; w / wo, With or without *denotes significance at the p<0.05 level				

Figure 4.1: Unweighted survival curve and number at risk

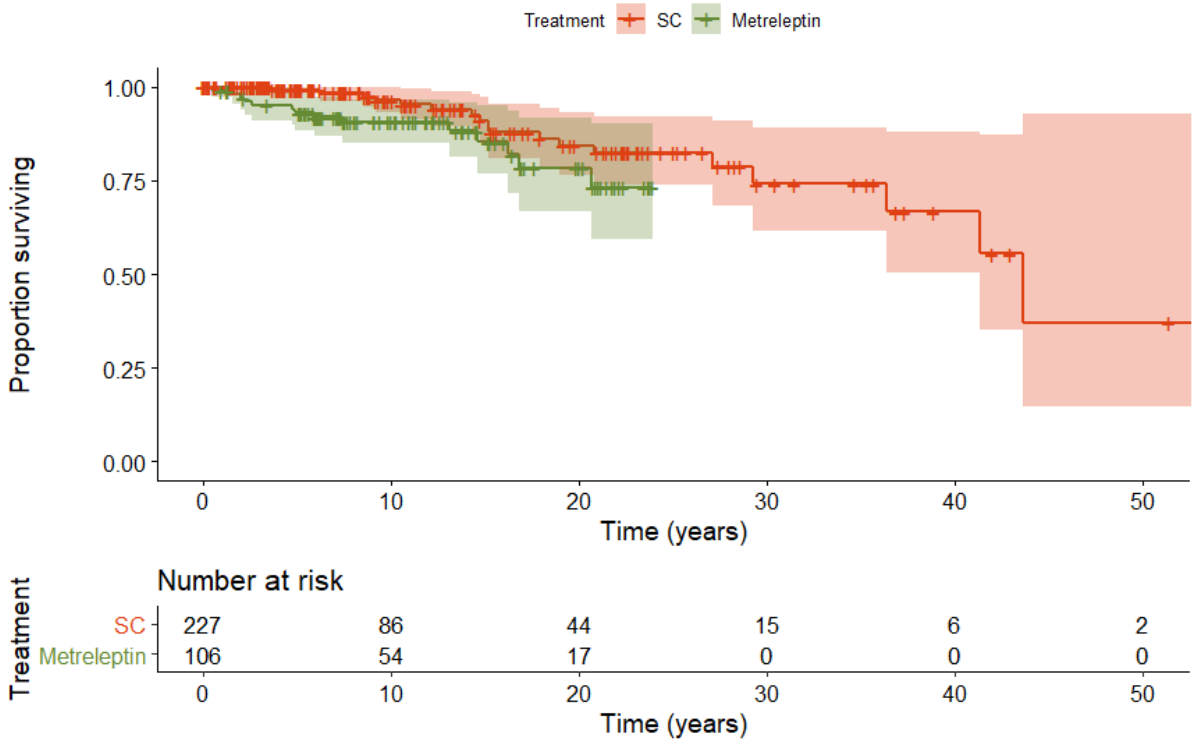
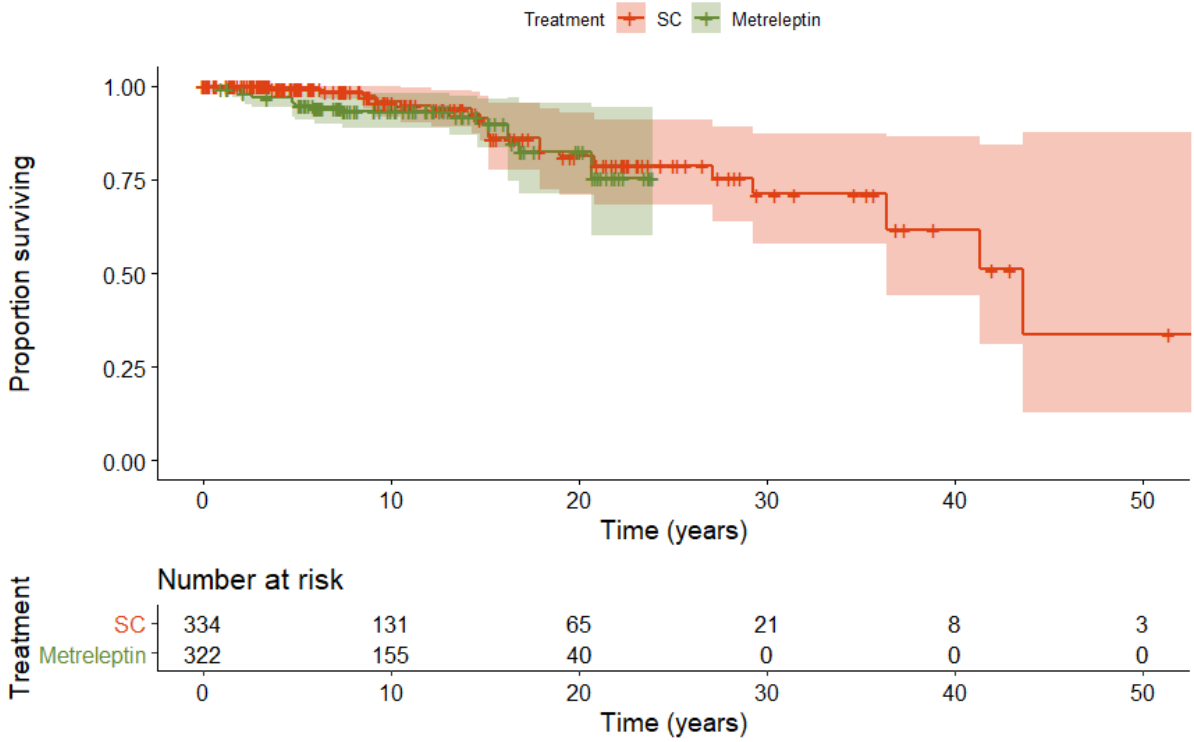


Figure 4.2: Weighted survival curve and number at risk



The company also presented the R^2 value and Q-Q plots to assess normality for each of the regression analyses. On the basis of the low R^2 value, which was never higher than 0.135 and the Q-Q plots, the company confirmed the unsuitability of the regression analysis method.

An assessment of covariate balance was also presented in Section 17.12.5 of the CS,[1] for each of the outcomes and for each of the three covariates, age, gender and lipodystrophy type, by three methods: summary statistics, density plots and three statistics, standardised mean difference (SMD), variance ratio (VR) and Kolmogrov-Smirnov (KR) test. A summary of the statistical assessment is shown in Table 4.29.

Table 4.29 Summary of assessment of covariate balance following adjustment using IPW

Outcome	**Age**	**Gender**	**Lipodystrophy type**
HbA1c	Remained unbalanced, except VR	Remained unbalanced	Remained balanced
Triglycerides	Achieved/ remained balanced, except KS	Achieved balance	Achieved balance
ALT	Achieved/ remained balanced, except KS	Remained balanced	Achieved balance
AST	Achieved/ remained balanced, except KS	Remained balanced	Achieved balance
Acute pancreatitis	Achieved/ remained balanced, except KS	Achieved balance	Achieved balance
All-cause mortality	Achieved/ remained balanced, except KS	Achieved balance	Achieved balance
Abbreviations: VR, variance ratio; KS, Kolmogrov-Smirnov			

ERG comment: The disparity in baseline characteristics between the two sources of data, the NIH follow-up and the GL/PL Natural History Study (see Section 4.2.1) clearly indicated the need to attempt to adjust for confounding. Following several methods to perform this adjustment, the results show a clear advantage to metreleptin for all outcomes assessed except for all-cause mortality. The tests of covariate balance showed varying degrees of success using the IPW method of adjustment with least success for HbA1c. However, it is likely that better balance would not favour metreleptin, for most outcomes, given that any of the form of adjustment essentially made little difference to the treatment effect favouring metreleptin. Indeed, for acute pancreatitis the treatment effect decreased and for all-cause mortality the adjustment merely reduced the numerical disadvantage for metreleptin.

Given the range of different methods of analysis employed in the ITC and the lack of apparent change relative to the naïve comparison, it might be reasonable to conclude that the results of the ITC are robust. It should also be noted that that the ITC was based on all PL patient data from the NIH follow-up study, the outcomes for which were generally worse than the data for the PL subgroup, who are probably more consistent with the license.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work to obtain data from technical reports undertaken by the ERG has been included in Section 4.2.4 of this report. No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 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, although 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 except in the ITC section and only for a limited set of outcomes, even though this study was used in the cost effectiveness analyses presented. This necessitated the obtaining of data, by the ERG, from a technical report.[45] Evidence for the comparator from the GL/PL Natural History Study also had to be obtained from another technical report.[43]

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

A 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 to one year in single arm studies. There was limited reporting of the GL/PL natural history study, used to provide comparator data, although the ERG was able to obtain all of the available data from the technical report. However, the population of the GL/PL Natural History Study was not comparable to the NIH studies, as indicated by the different baseline characteristics and use of lipid lowering drugs and anti-diabetic medications, to those included in the metreleptin intervention studies. It is therefore difficult to assess the extent to which any apparent treatment effects are attributable to metreleptin.

A further substantive issue concerns the nature of the treatment effects reported. The CS focuses primarily on changes in surrogate outcome measures (e.g. HbA1c, triglycerides, hepatic enzymes) and includes very little information about any effects of treatment on patient-perceived symptoms and

clinical outcomes e.g. hyperphagia and organ damage, other than pancreatitis. The report of the NIH follow-up study,[45] 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 were frequently based on measures taken at one year and used definitions based on changes in surrogate outcome measures; for example, improvement in liver abnormality is defined as 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, 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 HbA1c, 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.

The company has made attempts to mitigate the problem of lack of comparability between studies by the conduct of an ITC with a method of adjustment to control for confounding. This is still limited, in that it mostly pertains to surrogate measures of outcome i.e. HbA1c, triglycerides, ALT and AST, although acute pancreatitis and all-cause mortality were included. The methodology of the ITC was based on recommendations by the NICE DSU in the form of TSD 17 and two different methods of adjustment, IPW and multiple regression analysis, were compared with a naïve comparison. Various methods of assessment provided some evidence to favour IPW over multiple regression analysis and the naïve comparison. The difference the adjustment made varied between outcomes. The treatment effect essentially changed little and favoured metreleptin for all continuous outcomes. For pancreatitis the treatment effect favouring metreleptin decreased with the IPW method. For all-cause mortality, the treatment effect favouring supportive care decreased relative to the naïve comparison, but with a rise in uncertainty, as reflected by a larger p value.

4.6.3 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,[45] included some information on newly emergent (on metreleptin treatment) lipodystrophy characteristics in patients with no evidence of these characteristics prior to metreleptin initiation. 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.

There is some uncertainty regarding the applicability of the ITC results to UK clinical practice. Data from all PL patients as opposed to the PL subgroup, which is more likely to be aligned with the license, were used. However, given that outcomes were generally better for the subgroup, the effect of this mismatch is likely to have been conservative. On the other hand, the outcomes that were co-primary, triglyceride and HbA1c changes, were worse for the Addenbrooke's EAP than the NIH 991265/20010769 study and also the NIH follow-up study results that were used in the ITC and thence in the CEA. Given that the EAP includes only UK patients at Addenbrooke's Hospital, it may be that changes in some outcomes, observed in the NIH studies, might not be realised in UK clinical practice. On reflection, the ERG would therefore recommend consideration of the performance of the ITC using data from the EAP, particularly for HbA1c and triglycerides.

It is unclear what criteria will be used to determine which patients with PL will receive metreleptin treatment. The EMA marketing authorisation, for PL, is for adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. The CS indicates that the company considers that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is the PL population most considered to best reflect the licensed indication. Leptin levels were part of the PL subgroup definition in NIH studies 991265/20010769, via the inclusion criteria (NIH 2001769: <12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years; NIH 991265: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males). The PL subgroup population in the Addenbrooke's EAP (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is therefore similar to that in the NIH studies 991265/20010769. It should be noted, however, that some PL patients who did not meet these baseline metabolic criteria have been treated in the Addenbrooke's EAP.

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.[55] 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 hypoglycaemia, autoimmunity, and hypersensitivity.'[55]

5. VALUE FOR MONEY FOR THE NHS AND PSS

5.1 Introduction

This chapter aims to provide an assessment of whether metreleptin for lipodystrophy represents value for money for the NHS in England. The main source of evidence used to inform this assessment is the company submission and cost effectiveness model. This chapter will provide a summary of: the literature review performed by the company to search for economic evidence, the structure of the company model, the evidence used to inform the economic analyses and the results of the company analyses, as well as a critique of these aspects by the ERG.

5.2 Review of existing economic analyses

The company conducted a systematic literature review in order to identify published economic evaluations, utility, and cost and resource use studies .[1] Details of the SLR search strategies were provided in Sections 17.3-17.5 (Appendices 3-5) of the company submission respectively.[1]

5.2.1 Searches

Sections 17.3, 17.4 and 17.5 (Appendices 3, 4 and 5) detail the SLR and search strategies conducted to identify all literature published on economic evaluations, utility, and cost and resource use studies. The search was conducted on 16 October 2019 and is an update of the searches used in the previous submission.[62] The date span of the search was reported as 2006 to 16 October 2019, however the reported searches were limited to 2017 to search date and the 2006 start date refers to the search from the previous submission, the results of which were taken into account here. The selection of databases searched was adequate (Medline, Medline in Process, EMBASE, Centre for Reviews and Dissemination (CRD) HTA and NHS Economic Evaluation Database (EED), and the EuroQol database), all database searches were reported in the CS and in the response to clarification[37] and for the most part were reproducible. A summary of the sources searched is provided in Table 5.1.

Table 5.1 Data sources for the cost effectiveness systematic review (as reported in CS)

Search strategy element	Resource	Host/source	Date range	Date searched
Electronic databases	Embase	Embase.com	October 2006 to October 2019	16 October 2019
	MEDLINE and MEDLINE In-Process	Embase.com	October 2006 to October 2019	16 October 2019
	Centre for Reviews and Dissemination (CRD) Health Technology Assessment (HTA) and National Health Service (NHS) Economic Evaluation Database (EED)	CRD Website	2017 to 2019	16 October 2019

	EuroQol Database	Not reported	2017 to 2019	16 October 2019
Conference proceedings	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Not reported	Not Reported	16 October 2019
	European Conference of Endocrinology (ECE)			
	International Conference on Metabolic Syndrome			
	International Conference on Endocrinology			
Websites	HTA Agencies (see 17.3.5 of the CS for full list)[1]	Not reported	Not reported	16 October 2019
	Google Scholar			
CRD = centre for reviews and dissemination; CS = company submission; ECE = European conference of endocrinology; EED = economic evaluation database; HTA = health technology assessment; ISPOR = international society for pharmacoeconomics and outcomes research; NHS = national health service.				

ERG comment:

- A single search was undertaken for economic evaluations, cost and resource use studies and health state utility values. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources.
- Study design filters in the Embase.com search were appropriately used and based on terms designed by the Scottish Intercollegiate Guidelines Network (SIGN) and York Health Economics Consortium (YHEC).
- The CRD and EuroQol search strategy had some errors (the term lipodystrop was used and no truncation symbol employed) and unnecessarily included economics terms when this resource is already filtered for those types of studies (more details of the errors are provided in Appendix 1 of this report)
- Reporting of the grey literature searches could have benefited from the addition of more details to make the searches more transparent and reproducible.

5.2.2 Review process and results

The inclusion exclusion criteria used in the search for economic evidence, resource use and costs and HRQoL evidence are outlined in Tables 65, 66 and 67 of the company submission.[1]

The CS displays the schematic for the updated economic evidence, resource identification and HRQoL SLRs.[1] No publications were identified from the updated economic SLR. The PRISMA diagram for the previous submission can be found in Figure 37 of the CS. The previous economic SLR retrieved a total of three studies, none of which were relevant to economic evaluation of metreleptin. All three 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 submission owing to the population studied.

The reporting of the results of the updated resource use SLR refers only to Figure 22 of the CS which displays the schematic for the updated economic evidence, resource identification and HRQoL SLRs.[1] The company then goes on to state that the previous submission found only studies related to HIV-associated lipodystrophy, which is outside of the scope for the submission, and was therefore not considered relevant resource data.[1]

The reporting of the updated HRQoL SLR again refers to Figure 22 and states that the previous SLR found two HRQoL references for data extraction (PRISMA diagram shown in Figure 38 of the CS).[1] The next section states that one publication reporting HRQL was identified in the SLR, which is presumably the only additional study identified across the three updated SLRs in Figure 22 of the CS. This study, by Ali et al., conducted a discrete choice experiment (DCE) with 1,000 members of the general population, in order to characterise the health utility consequences of GL and PL patients, as well as assess the QALY gains associated with leptin replacement therapy (metreleptin).[63]

In all three SLRs, the relevant data from the included studies were extracted into predefined data extraction tables by one analyst. All the data points were verified in a quality check by a second analyst.

ERG Comment: On the whole the criteria seem reasonable, although the exclusion of non-English language papers may have included publication bias. In the HRQoL SLR, studies reporting results from quality-of-life measures that are not on reported on scale of 0-1 were excluded. This is not necessarily an appropriate exclusion criterion as such HRQoL data could have potentially been mapped to a preference based 0-1 scale and therefore useful HRQoL studies may have been missed due to this criterion.

The reporting of the number of studies included in each of the updated SLRs was unclear, as the results were combined into a single figure and then not thoroughly explained in text. Therefore, it was difficult for the ERG to assess whether the update was completed well or any studies were missed.

5.3 Exposition of the company's model

5.3.1 Economic evaluation scope

Table 5.2 below provides an assessment of the adherence of the company model to the NICE reference case.

Table 5.2 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	As per reference case
Comparator	Therapies routinely used in the NHS, including technologies regarded as the current best practice	Standard of care (SoC) is the only comparator as per the scope.[32] SoC represents established clinical management without metreleptin (including diet and lifestyle modifications, lipid lowering drugs and medications for diabetes).

Element of economic analysis	Reference case	ERG comment
Perspective on costs	NHS and PSS	NHS and PSS perspective adopted in line with reference case
Perspective on outcomes	All health effects on individuals.	Health effects on individuals and carers included
Type of economic evaluation	Cost-effectiveness analysis	As per reference case
Time horizon	Sufficient to capture differences in costs and outcomes	Lifetime perspective adopted. 100 annual cycles were included in the model to ensure that each patient would experience a lifetime horizon. All patients died within the model time horizon
Synthesis of evidence on outcomes	Based on a systematic review	Updates to the previously reported systematic reviews for economic, cost and resource use and HRQoL evidence
Measure of health effects	QALYs and life years	Health outcomes are valued in terms of life years and QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Various sources of utility values used. Disutilities for organ sub-model complications sourced from various literature sources related to each specific organ condition. Utility decrements for pancreatitis and other lipodystrophy specific symptoms (e.g. hyperphagia) sourced from a DCE study which estimated disutilities for lipodystrophy complications and symptoms valued by general population samples in 6 countries including the UK. The disutility associated with caring measured using the EQ-5D directly in carers and valued using the UK EQ-5D-3L preference weights.
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.	As per reference case
Equity weighting	An additional weighting can be applied for incremental QALYs above 10 years.	The company adjusted the ICER according to the NICE HST process guide to reflect the significant QALY gains (>10 incremental undiscounted QALYs) for treated patients.[64]

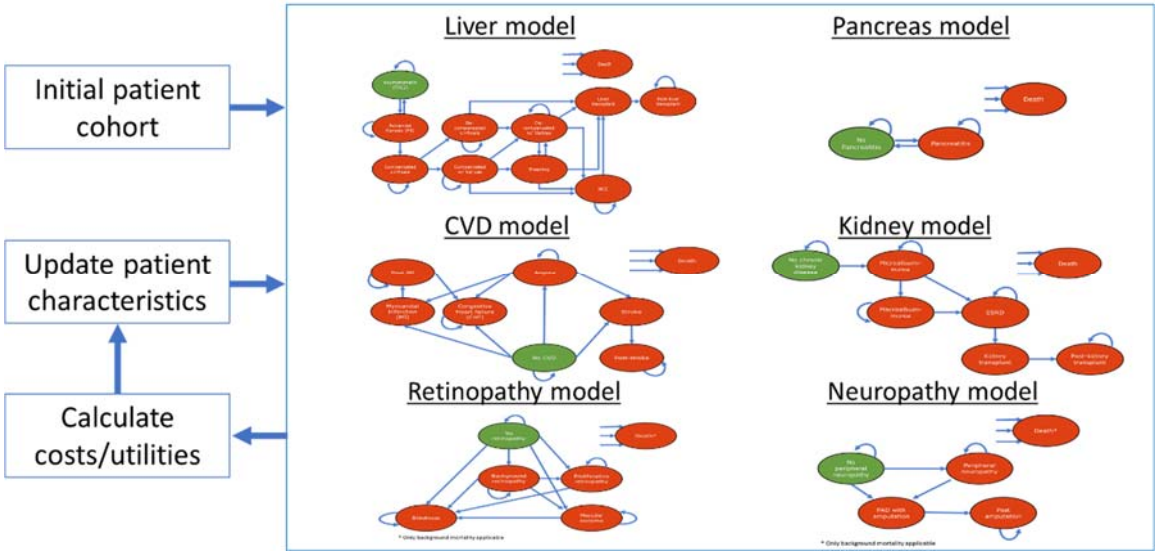
Element of economic analysis	Reference case	ERG comment
DCE = discrete choice experiment; EQ-5D-3L = EuroQoL - 5 dimensions - 3 levels; HRQoL = health-related quality of life; HST = highly specialized technology; ICER = incremental cost effectiveness ratio; NHS = national health service; NICE = national institute of health and care excellence; PSS = personal social services; QALY(s) = quality-adjusted life year(s); SoC = standard of care; UK = United Kingdom.		

5.3.2 Model structure

A de novo individual patient level model was constructed aiming to address prior concerns raised by the NICE committee.[65] This model was developed in collaboration with clinical experts in order to better reflect the progression and clinical management of the disease.[1]

The model, shown in Figure 5.1, consists of six Markov sub-models simulating the progression of disease on distinct organ systems affected by lipodystrophy, capturing the key lipodystrophy-related complications which impact health-related quality of life, costs and mortality over the lifetime of lipodystrophy patients.[1] The organ sub-models included are: pancreas, liver disease, cardiovascular disease, kidney, neuropathy and retinopathy. In each simulation in each cycle (cycle length one year), a patient is simultaneously in a single discrete health state in each of the six independent organ sub-models. A patient can die during each cycle, in which case the patient is removed from all sub-models into the death state. More detail about each sub-model is provided below.

Figure 5.1: Individual patient-level model structure

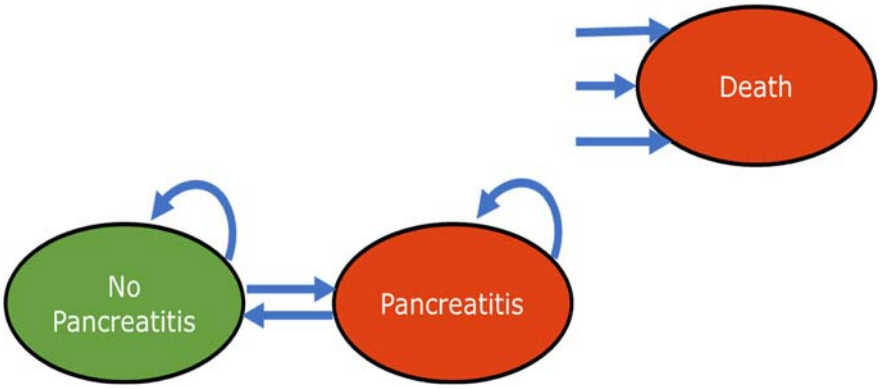


Source: Figure 23 in the CS.[1]
CS = company submission; CVD = cardiovascular disease.

5.3.2.1 Pancreas sub-model

As described in the company submission and supported by clinical experts, GL and PL patients are at higher risk of pancreatitis, especially those with raised triglyceride levels. The pancreas sub-model, shown in Figure 5.2 contains three health states: No pancreatitis, pancreatitis and death.

Figure 5.2: Pancreas sub-model structure

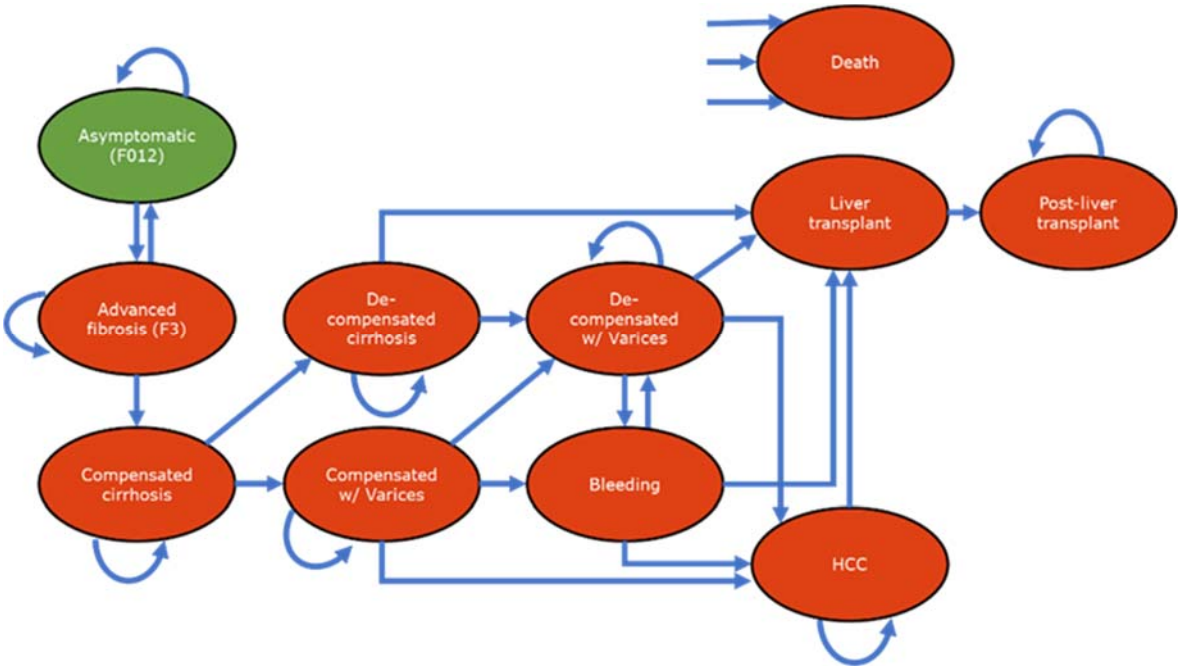


Source: Figure 24 in the CS.[1]
CS = company submission

5.3.2.2 Liver sub-model

Clinical experts also supported the proposition that lipodystrophy patients are at risk of non-alcoholic fatty liver disease (NAFLD) (specifically NASH), as a result of ectopic fat deposition, leading to the development of complications such as cirrhosis and hepatic cell carcinoma. Therefore, the liver sub-model models liver disease complications as mediated by lipodystrophy using the pathogenesis of NAFLD/NASH as an analogue for lipodystrophy patients suffering from liver disease. The model structure, shown in Figure 5.3 below, is based on the *de novo* cost effectiveness model developed for the NICE NAFLD guideline (NG49).[66]

Figure 5.3: Liver sub-model structure



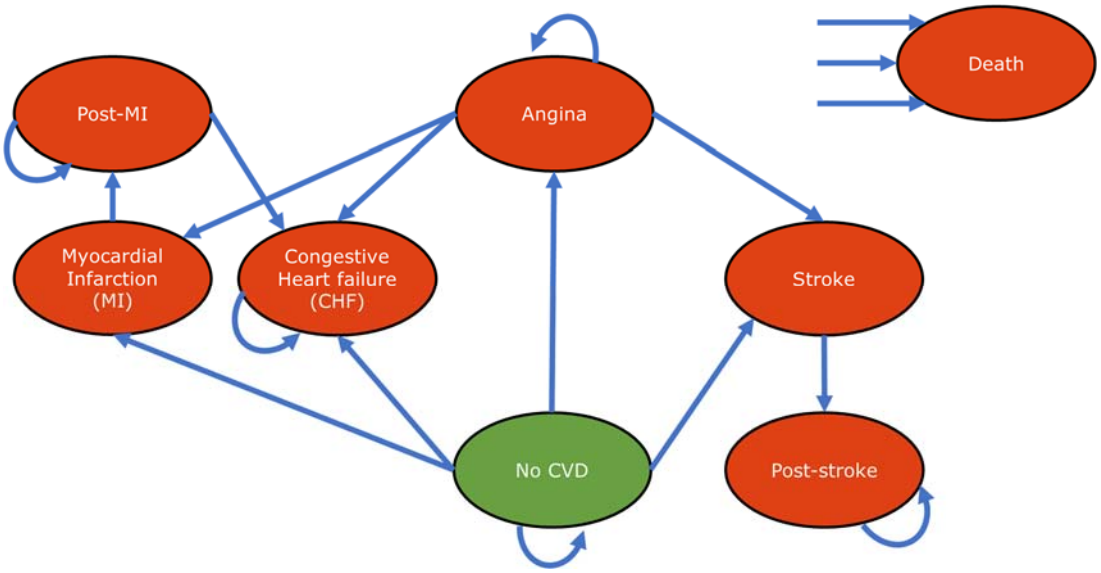
Source: Figure 25 in the CS.[1]
CS = company submission; F = fibrosis; HCC = hepatic cell carcinoma.

Patients transition through health states, from having no or asymptomatic fibrosis, to advanced fibrosis to compensated and then de-compensated cirrhosis. Advanced fibrosis is reversible, and patients can therefore transition from advanced fibrosis to asymptomatic disease. Compensated and decompensated cirrhosis can worsen to become compensated or decompensated cirrhosis with varices (respectively), and from those states patients can transition to bleeding (one-off event) and HCC (hepatocellular carcinoma). Patients can also undergo liver transplant from decompensated cirrhosis, bleeding or HCC. The transplant state represents the acute surgical phase, while the post-transplant state models patients' long-term health after transplant. With the exception of the transplant state, the health states in the liver model are all continuous, meaning patients can remain within any of the health states for more than 1 cycle. Patients can die from any health state, with the decompensated cirrhosis, bleeding and HCC states associated with elevated mortality risks.[1]

5.3.2.3 Cardiovascular sub-model

As described in the company submission and supported by clinical experts, GL and PL patients are also at higher risk of cardiovascular disease, particularly those with hypertriglyceridaemia and diabetes (i.e. elevated HbA1c).[67] The model health states included in the CVD sub-model, shown in Figure 5.4, are based on a review of previously accepted NICE models for CVD and the literature, in order to reflect the common complications observed in lipodystrophy patients.[68-70]

Figure 5.4: Cardiovascular sub-model structure



Source: Figure 26 in the CS.[1]
CHF = congestive heart failure; CVD = cardiovascular disease; MI = myocardial infarction.

The aim of the CVD model is to simulate the incidence of angina, congestive heart failure (CHF), myocardial infarction (MI) and stroke as these complications were the most prominent in previous cardiovascular models and most commonly experienced by lipodystrophy patients.[1, 2] Although patients are also at risk of cardiomyopathy, this was not included due to a lack of transition probability data identified in the literature.

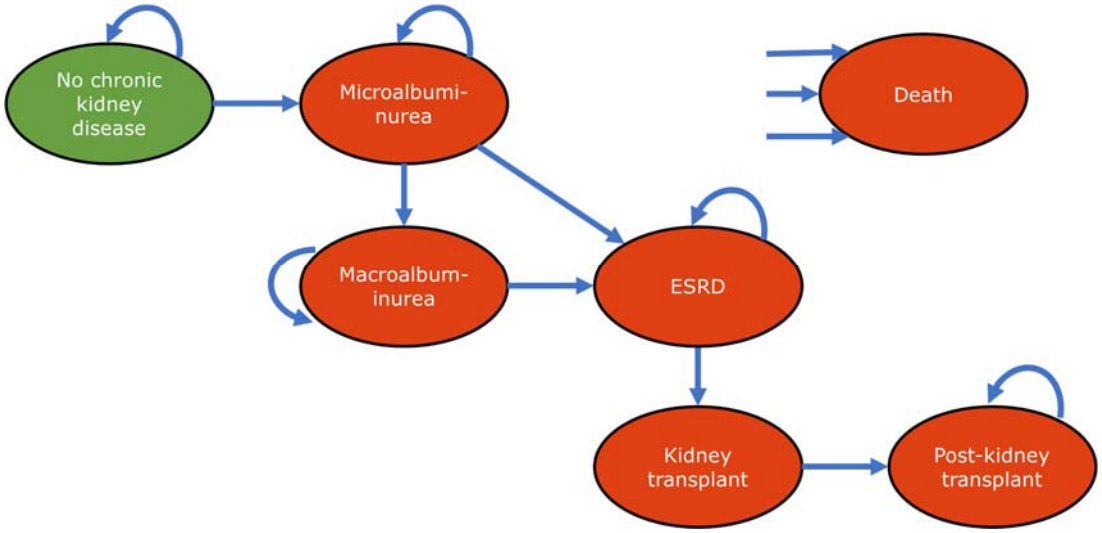
Patients start the CVD model in the No CVD state, where they are at risk of experiencing cardiovascular complications in each cycle.[1] The MI and stroke health states are tunnel health states representing the acute stage (including rehabilitation) of the condition, with patients subsequently state moving to the

post-MI and post-stroke health states, which represent the long-term maintenance of the condition. Patients may enter the stroke or MI states only once, but can remain in the continuous post-event states (Post-MI, Post-stroke and CHF). Patients can die from cardiovascular conditions from any health state except No CVD (and from background mortality regardless of state), with patients at an elevated risk of mortality from more severe CVD health states.

5.3.2.4 Kidney sub-model

The company also state that GL or PL patients are at also are at a higher risk of kidney disease, especially those with diabetes (i.e. elevated HbA1c), as validated by clinical experts.[67] The kidney sub-model structure, shown in Figure 5.5, reflects the common renal complications associated with lipodystrophy. This structure is consistent with the structure of the Sheffield diabetes model and has been validated with UK clinical experts.[68]

Figure 5.5: Kidney sub-model structure



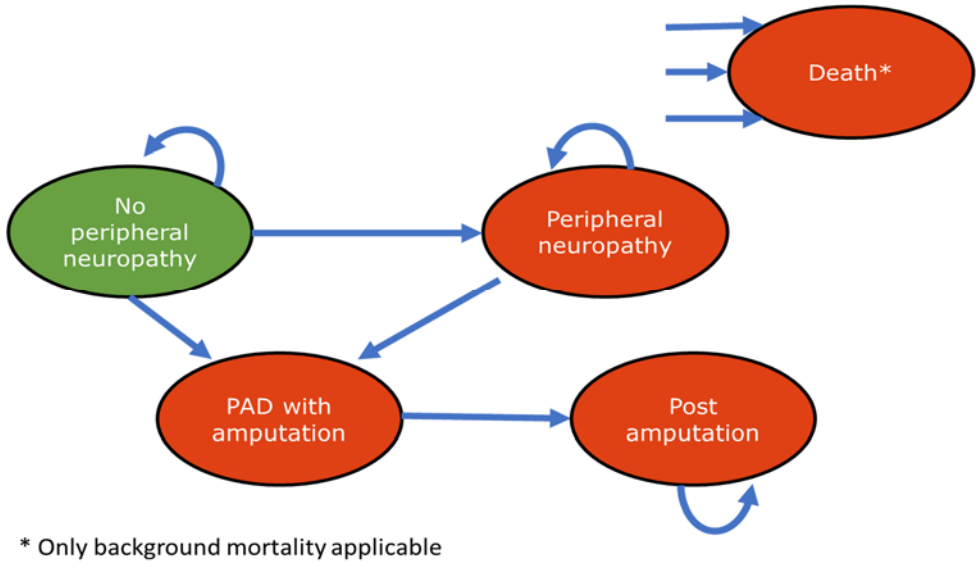
Source: Figure 27 in the CS.[1]
CS = company submission; ESRD = end stage renal disease.

Patients begin in the no chronic kidney disease state, where they can remain or from where they transition through microalbuminuria and macroalbuminuria to the end stage renal disease (ESRD) health state. From ESRD patients can transition to receiving a kidney transplant (tunnel state), moving to the post-transplant state in the following cycle. Patients can die from kidney related complications from any health state, and from background mortality from any state.[1]

5.3.2.5 Neuropathy sub-model

The company and clinical experts also state that GL and PL patients are at higher risk of neuropathic disease, especially those with diabetes (i.e. elevated HbA1c).[67] The neuropathic disease sub-model structure, displayed in Figure 5.6, reflects the neuropathic and peripheral vascular specific elements of microvascular complications associated with lipodystrophy.[1] This sub-model includes four health states; no peripheral neuropathy, peripheral neuropathy, peripheral arterial disease (PAD) with amputation and death. Patients can remain in any of the alive health states in each cycle except the PAD with amputation tunnel state. Patients can die from any health state based on background mortality rates.

Figure 5.6: Neuropathy sub-model structure

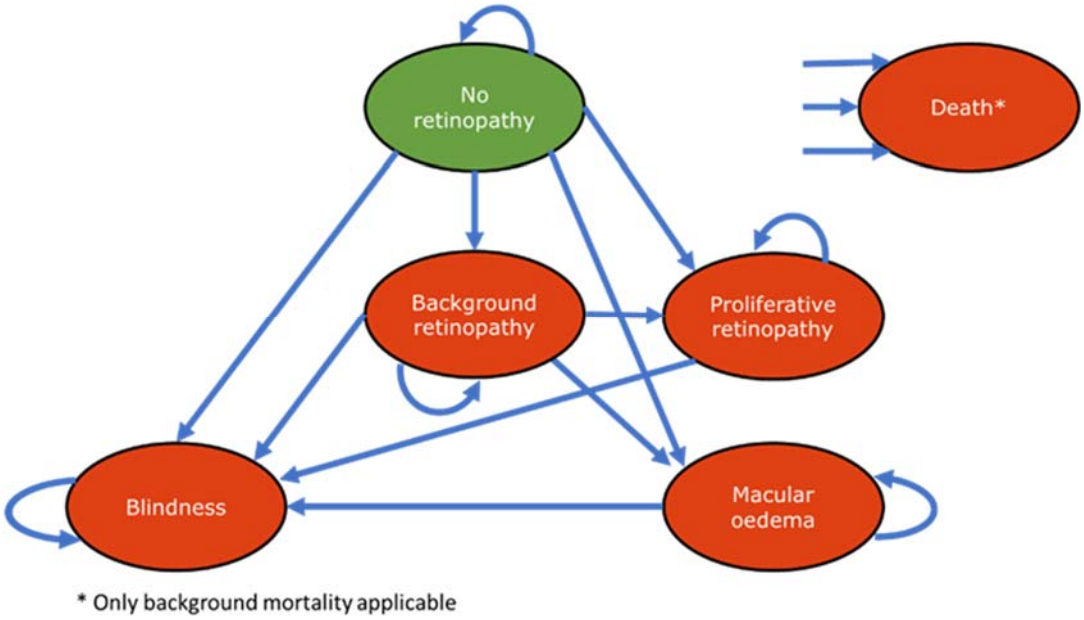


Source: Figure 28 in the CS.[1]
PAD = peripheral arterial disease.

5.3.2.6 Retinopathy sub-model

GL and PL patients are at are at higher risk of retinopathy, especially those with diabetes (i.e. elevated HbA1c), as validated by clinical experts.[67] The retinopathy sub-model, shown in Figure 5.7, simulates retinopathy-specific microvascular complications associated with lipodystrophy.[1] Patients enter the sub-model with no retinopathy and can progress to blindness either directly, or by progressing through various retinal diseases such as background retinopathy, proliferative retinopathy and macular oedema. Patients can remain within any of the alive health states in each cycle. Patients can die from any health state based on background mortality rates.[1]

Figure 5.7: Retinopathy sub-model structure



Source: Figure 29 in the CS.[1]

ERG comment: The company reported in the CS that the NICE committee had expressed concerns about the previous two cost effectiveness models submitted in relation to this appraisal as they felt that disease progression of lipodystrophy over time was not reflected in the model.[1] The committee acknowledged that evidence in the area of lipodystrophy was sparse but noted that metabolic, surrogate outcomes could be used to extrapolate outcomes in the model, and a diabetes or fatty liver model basis would be more appropriate to use for the model. The submitted model structure does reflect those suggestions by the committee and is an improvement on previous submissions as it is better structured to account for the potential progression of complications related to lipodystrophy over time. However, it remains predicated upon the assumption that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but different aetiology. This is an area of considerable uncertainty.

5.3.3 Evidence used to inform the company's model parameters

Table 5.3 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 section 12.2.[1]

The initial patient distribution is based on the baseline characteristics from the NIH studies, both for SC and metreleptin arms. The proportion of patients with GL or PL were derived from the Addenbrooke's EAP data.

The discontinuation rate is based on the annual discontinuation rate for treatment non-compliance from the NIH studies.

Table 5.3 Summary of evidence sources used to inform key parameter groups in the company's model

Sub-model	Source of baseline model transitions	Outcomes used to drive transition changes	Relative clinical effectiveness between metreleptin and SC approach	Mortality inputs (besides all-cause mortality)
Pancreas	GL/PL Natural History study [22]	Hard outcome – pancreatitis.	ITC	NICE pancreatitis guidance [71]
Liver	NICE NAFLD guideline[66]	Not applicable in the base case. A scenario analysis using ALT and AST (liver enzymes) as surrogates to estimate risk of advanced fibrosis from asymptomatic health state based on risk equation from Hossain *et al.* [72]	Base case: Delphi panel (directly estimated the risk reduction in liver disease complications in metreleptin-treated compared to SC-treated patients). Scenario analysis: Change in ALT and AST from baseline taken from the indirect treatment comparison (see CS section 9.8).	NICE NAFLD guideline [66]

Sub-model	Source of baseline model transitions	Outcomes used to drive transition changes	Relative clinical effectiveness between metreleptin and SC approach	Mortality inputs (besides all-cause mortality)
Cardiovascular	DCCT / EDIC study; Sheffield diabetes model.[68, 73, 74] Risk of complications adjusted for relative risk of CVD complications for type 1 diabetes compared to early-onset type 2 diabetes[75, 76]	The Delphi panel concluded that HbA1c is a good predictor of CVD outcomes in lipodystrophy patients [67] and relationship with hard outcomes is established. As such, surrogate outcome of HbA1c employed.[74, 77]	Change in HbA1c from baseline used from NIH studies 991265/200110769 [52]; ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data	Smith *et al.* [70]
Kidney	DCCT; Wong *et al.*; UKPDS 33; Sheffield diabetes model; NICE TA358.[68, 77-80] Risk of complications adjusted for relative risk of ESRD for type 1 diabetes compared to early onset type 2 diabetes. [81]	The Delphi panel concluded that HbA1c is a good predictor of kidney disease outcomes [67] and relationship with hard outcomes is established. As such, surrogate outcome of HbA1c employed.[80, 82, 83] Adjusted using the Eastman's' method. [84]	Change in HbA1c from baseline used from NIH studies 991265/200110769 [52]; ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data.	Sheffield diabetes model.[68]
Retinopathy	WESSR XXII, Sheffield diabetes model.[68, 82]	The Delphi panel concluded that HbA1c is a good predictor of retinopathy outcomes [67] and relationship with hard outcomes is established. As such, surrogate outcome of HbA1c employed.[82] Adjusted using the Eastman's' method.[84]	Change in HbA1c from baseline used from NIH studies 991265/200110769 [30]; ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data.	Not applicable.
Neuropathy	DCCT; Moss *et al.;* Sheffield	The Delphi panel conducted concluded that	Change in HbA1c from baseline used from NIH studies	Not applicable.

Sub-model	Source of baseline model transitions	Outcomes used to drive transition changes	Relative clinical effectiveness between metreleptin and SC approach	Mortality inputs (besides all-cause mortality)
	diabetes model.[68, 83, 85] Risk of complications adjusted for relative risk of neuropathy complications for type 1 diabetes compared to early onset type 2 diabetes.[75, 76]	HbA1c is a good predictor of neuropathy outcomes[67] and relationship with hard outcomes is established[80, 86, 87] As such, surrogate outcome of HbA1c employed. Adjusted using the Eastman's' method.[84]	991265/200110769[30]; ITC for pooled lipodystrophy population demonstrated observed reductions were representative of comparative data.	

Based on Table 41 of the CS.[1]
ALT = alanine transferase; AST = aspartate aminotransferase; CS = company submission; CVD = cardiovascular disease; DCCT = diabetes control and complications trial; EDIC = epidemiology of diabetes interventions and complications; ESRD = end-stage renal disease; GL = generalised lipodystrophy; HbA1c = glycosylated haemoglobin type A1c; ITC = indirect treatment comparison; NICE = national institute of health and care excellence; NIH = national institute of health; PL = partial lipodystrophy; SC = supportive care; UKPDS = United Kingdom prospective diabetes study; WESSR = Wisconsin Epidemiologic Study of Diabetic Retinopathy.

5.3.3.1 Initial patient distribution

The patient population considered in the cost effectiveness model (CEM) analyses is aligned to the licensed indication for metreleptin,[46] and includes:

- Adults and children above the age of two years with generalised lipodystrophy (GL).
- Adults and children above the age of 12 years with partial lipodystrophy (PL), when standard treatments have failed to achieve adequate metabolic control.

The baseline characteristics representative of patients with GL and PL inputted in the model are summarised in Table 5.4. These were based on the NIH studies 991265/200110769. The company reported a lack of published data concerning the prevalence and incidence of GL and PL relevant to the licensed metreleptin population.[1] The company used the distribution of GL and PL patients from the Addenbrooke's EAP data, assuming that patients at this centre will be representative of eligible patients in the UK clinical practice (response to B1.[37]).

Table 5.4 Baseline characteristics, patients with GL and PL

	Type of lipodystrophy	
	GL	**PL**
Lipodystrophy type (%)	43.48%	56.52%
Female (%)	77.3 %	96.8 %
Mean age (years) [SD]		37.0 [14.37]
Male	19.5 [18.10]	
Female	17.3 [17.3]	

HbA1c (%) [SD]		8.8 [1.88]
Male	8.1 [2.52]	
Female	8.8 [2.25]	
Weight (kg) [SD]		68.7 [14.67]
Male	55.1 [20.22]	
Female	51.9 [18.58]	
Source: Table 37 in the CS.[1] GL = generalised lipodystrophy; PL = partial lipodystrophy; HbA1c = glycosylated haemoglobin type A1c; kg = kilogram; SD = standard deviation.		

ERG comment: The patient population used in the ITC differs from the patient population used in the CEM. The ITC was performed on all PL patients whilst the patients' characteristics in the model are based on the PL subgroup, i.e. patients with baseline HbA1c>=6.5% and/or TG >=5.65 mmol/L. This was confirmed by the company in their response to clarification questions A36, where the company indicated that a subgroup analysis for the lipodystrophy sub-populations was not feasible due to sample size constraints.[37] Moreover, the company assumed that the prevalence of GL and PL patients observed in the EAP programme in the UK is representative of eligible patients in the UK (answer to question B1).[37] Based on the data reported in Table 36 in the CS[1], the ERG recognised that the patient distribution is based on the EAP data from Addenbrooke's Hospital in 2020, that is [redacted] GL and [redacted] PL patients (Table 5 in answer to clarification question A8 part 1).[37] The company did not specify whether the latter are part of the PL subgroup. The ERG has concerns as the PL subgroup, as specified in the CSR of the NIH studies, has the more severe metabolic abnormalities. This might result in a different outcome compared to a population including subjects with less severe metabolic abnormalities. It appears that the patients' characteristics are from the safety analysis set (SAS) which includes 66 GL and 41 PL (31 PL subgroup) whilst the treatment effect is evaluated in the full analysis set (FAS) which includes 62 GL and 40 PL (30 PL subgroup). The PL overall group is also on average younger in both the SAS and FAS (Table 5.5).

The ERG ran a scenario analysis using the patients' characteristics of the FAS and the overall PL. The results are shown in section 6.4.

Table 5.5 Patient demographics by analysis population and type of lipodystrophy

	SAS			**FAS**		
	Type of lipodystrophy			**Type of lipodystrophy**		
	GL (N=66)	**PL Subgroup (N=31)**	**PL Overall (N=41)**	**GL (N=62)**	**PL Subgroup (N=30)**	**PL Overall (N=40)**
Female (%)	77.3%	96.8%	97.6%	75.8 %	96.7 %	97.5%
Mean age (years)	17.8	37.0	34.1	17.0	37.1	34.1
Source: Table 11 and Table 14.1.2.1B in the CSR [52] SAS = safety analysis set; FAS = full analysis set; GL = generalized lipodystrophy; PL = partial lipodystrophy.						

5.3.3.2 Clinical parameters and variables

Given the limited availability of data in lipodystrophy, the company used published literature to obtain baseline transition probabilities for the liver, cardiovascular, kidney, neuropathy and retinopathy sub-models.[1] Diabetes-related baseline transition probabilities have been used for the diabetes-related

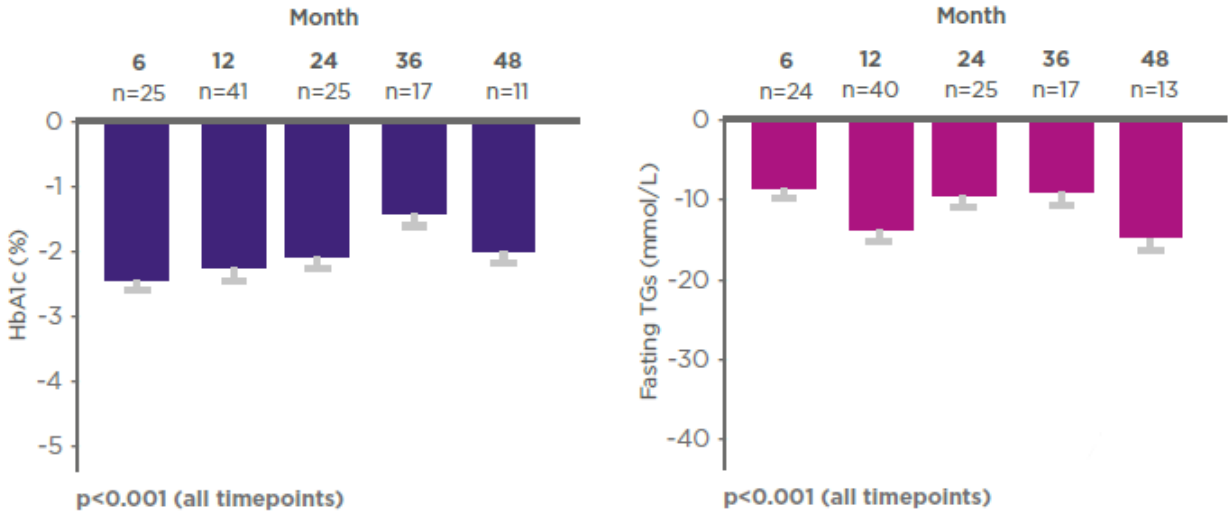
complications, i.e. cardiovascular, kidney disease, neuropathy and retinopathy. Liver baseline complications have been derived from the NICE NAFLD guideline model.[66]

HbA1c, triglycerides, liver enzyme (ALT and AST) levels and mortality were the only outcomes consistently captured and reported in the NIH studies and the GL/PL Natural History study. As such, these were the only outcomes considered feasible to include as outcomes of interest and were further deemed appropriate through clinician engagement.

Although organ abnormality was recorded as an outcome in both studies, there were discrepancies between the definitions. The only organ abnormality outcome assessed in the ITC analyses was incidence of acute pancreatitis which was consistently defined across the two studies. Fasting lipids and liver volume were not considered as outcomes of interest because, despite the fact these were recorded in the NIH 991265/20010769 study, the data were not available from the NIH follow-up study. An overall analysis of adverse events as an outcome was not deemed to be feasible due to differences in safety and tolerability definitions.

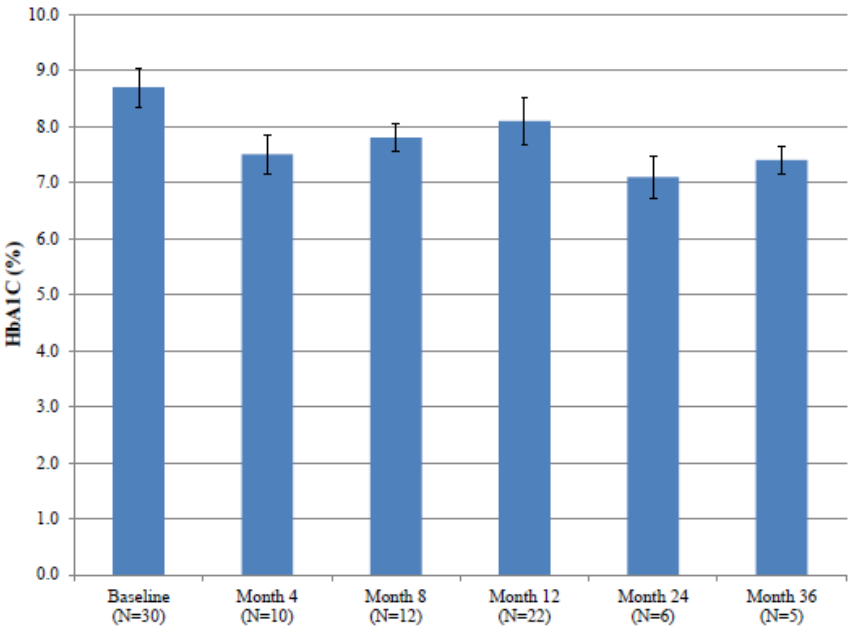
The change in HbA1c from baseline in patients treated with metreleptin was used to adjust the baseline transition probabilities to generate probabilities for the metreleptin cohort in the cardiovascular, kidney, neuropathy and retinopathy sub-models. Each patient entered the model with a baseline HbA1c level, based on the baseline levels from the NIH trials and their gender and type of lipodystrophy (GL or PL). Upon treatment initiation in the first cycle, patients receiving metreleptin experienced the full reduction in their HbA1c levels based on the change from baseline to 12 months observed in the NIH study. Thereafter, every cycle all patients in the model see a gradual rise in their HbA1c of 0.15% per year, regardless of whether they are on treatment with metreleptin, have discontinued from metreleptin or are receiving SC.[37] This 0.15% annual increase in HbA1c was assumed from a previous NICE appraisal in diabetes TA315 and is intended to reflect disease progression in diabetes.[88] This annual rise continues up to a ceiling HbA1c of 12%, based on clinical opinion from the Delphi Panel, according to which this plateau level would be representative of poorly controlled patients.[1] [67] The company argued that modelling HbA1c this way, the clinical benefits observed with metreleptin with respect to HbA1c reduction are sustained in the model while on treatment and partially post-discontinuation, as HbA1c continues to elevate over the model time horizon.[1] The company also reported that longer-term data has shown that HbA1c reductions observed with metreleptin have been sustained for at least 48 months.[1] Data relating to the long-term efficacy of metreleptin treatment showed clinically meaningful and statistically significant reductions in HbA1c and triglycerides in patients with GL and in the PL subgroup.[52] Mean HbA1c and triglyceride levels through month 48 in GL patients and month 36 in PL subgroup patients are shown in Figure 5.8 and Figure 5.9 below. It should be noted that this data shows HbA1c levels of patients still receiving metreleptin.

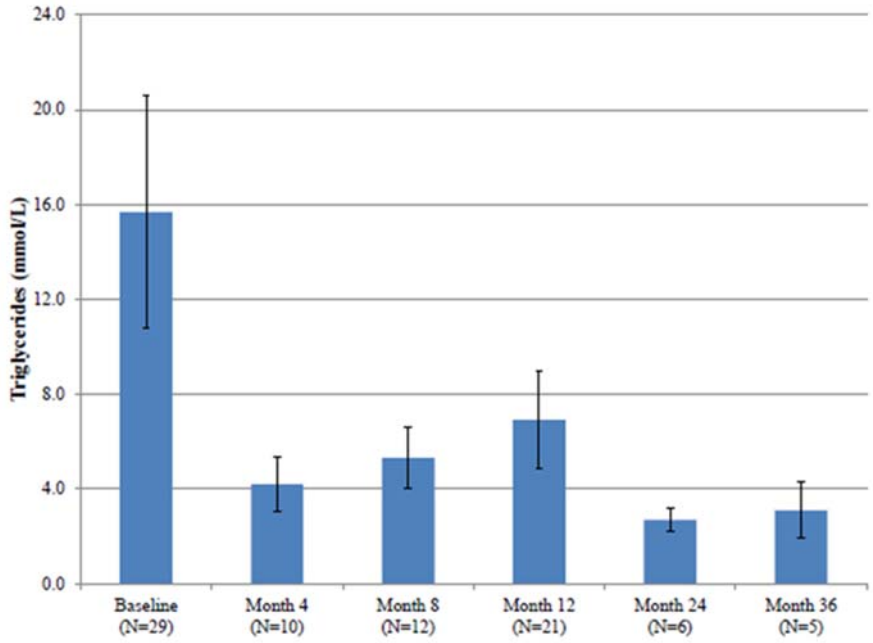
Figure 5.8: Mean (SEM) change in HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24, 36 and 48 of metreleptin treatment in NIH studies 991265/20010769 in GL patients



Source: Figure 15 of the CS [1]
GL = generalised lipodystrophy; HbA1c =glycosylated haemoglobin type A1c; L = litre; mmol = millimole; SEM = standard error of the mean; TGs = triglycerides.

Figure 5.9 - Mean (SEM) HbA1c (%) and triglycerides (mmol/L) at baseline and months 4, 8, 12, 24 and 36 of metreleptin treatment (FAS population) in NIH studies 991265/20010769 in PL subgroup patients





Source: Figure 16 of the CS [1]
FAS = full analysis set; HbA1c =glycosylated haemoglobin type A1c; L = litre; mmol = millimole; NIH = national institute of health; PL = partial lipodystrophy; SEM =, standard error of the mean;

The impact of a reduction in HbA1c levels on the risk of complications in the cardiovascular sub-model is based on data from the UKPDS study, a large prospective UK study in patients with type 2 diabetes.[89] This study calculated that an absolute reduction of HbA1c with 1%, is associated with a risk reduction of 14%, 12% and 16% for MI, stroke and heart failure, respectively. The relative benefits for the kidney, neuropathy and retinopathy models is driven through the model, as mentioned above, via the application of the Eastman's method which modulates the transition probabilities based on HbA1c levels in each cycle.[84]

Estimates of benefits for metreleptin-treated patients with respect to liver complications and disease progression compared to patients treated with supportive care were elicited from the Delphi panel in the base case [67]. An alternative method estimating the benefit for metreleptin-treated patients using ALT and AST as surrogates is explored by the company in a scenario analysis. This is based on applying the relationship between ALT and AST on predicting the risk of advanced fibrosis in a study by Hossain.[72] This is described further in section 12.2.3 of the CS.[1] Details on the transition probabilities are reported in the next section.

5.3.3.3 Transition probabilities

A summary of the clinical transition probabilities is reported in Table 5.6 a further narrative discussion of the transition probabilities can be found below the table.

Table 5.6 Clinical transition probabilities

Parameters	Transition probability	Source
Liver sub-model – Transition probabilities (unless stated otherwise), per cycle		
Asymptomatic liver disease to Advanced fibrosis	0.0533	NICE NAFLD guideline [66]
Advanced fibrosis to Asymptomatic liver disease	0.1057	
Advanced fibrosis to Compensated cirrhosis	0.0555	
Compensated cirrhosis to Compensated cirrhosis with varices	0.0604	
Compensated cirrhosis to Decompensated cirrhosis	0.0703	
Decompensated cirrhosis to Decompensated cirrhosis with varices	0.1266	
Decompensated cirrhosis to transplant	0.0228	
Compensated cirrhosis with varices to decompensated cirrhosis with varices	0.0703	
Compensated cirrhosis with varices to bleeding	0.1209	
Compensated cirrhosis with varices to HCC	0.0264	
Decompensated cirrhosis with varices to Bleeding	0.3163	
Decompensated cirrhosis with varices to HCC	0.0329	
Decompensated cirrhosis with varices to transplant	0.0228	
Bleeding to decompensated cirrhosis with varices	0.9376	
Bleeding to HCC	0.0369	
Bleeding to transplant	0.0256	
HCC to transplant	0.0408	
Asymptomatic liver disease to Death	0.	

Parameters	Transition probability	Source
Advanced fibrosis to Death	0.006	
Compensated cirrhosis/ compensated cirrhosis with varices to Death	0.02188	
Decompensated cirrhosis/ decompensated cirrhosis with varices to Death	0.215	
Bleeding to Death	0.2994	
HCC to Death	0.5604	
Transplant to Death	0.181	
Post-transplant to Death	0.0435	
Transplant to Post-transplant	1	Assumption
Risk ratio adjustment 'Asymptomatic liver disease to Advanced fibrosis' transition for SC patients	1.62146	Calculations using Hossain *et al.* and IPW from ITC. [72]
Risk ratio adjustment applied to metreleptin-treated GL patients	0.27	Delphi panel analysis
Risk ratio adjustment applied to metreleptin-treated PL patients	0.75	Delphi panel analysis
Cardiovascular sub-model – Transition probabilities (unless stated otherwise), per cycle		
Post-MI to CHF	0.0224	Smith *et al.* [70]
No CVD to MI	0.0113	Sheffield diabetes model, Calculations.[68]
No CVD to Angina	0.0060	
No CVD to CHF	0.0026	
No CVD to Stroke	0.0015	
Angina to MI	0.0113	Assumption, Sheffield diabetes model, Calculations.[68]
Angina to CHF	0.0026	
Angina to stroke	0.0015	
MI to Death	0.0713	Smith *et al.* [70]
Post-MI to Death	0.0286	
CHF to Death	0.43	
Stroke to Death	0.069	
Post-stroke to Death	0.236	

Parameters	Transition probability	Source
MI risk reduction per 1% reduction in HbA1c	14%	Stratton *et al*. [89]
Stroke risk reduction per 1% reduction in HbA1c	12%	
Heart failure risk reduction per 1% reduction in HbA1c	16%	
OR for CVD complications adjustment for early-onset type 2 diabetes vs compared to type 1 diabetes	2.04	Song *et al.* [75]
Kidney sub-model – Transition probabilities (unless stated otherwise), per cycle		
Healthy to Microalbuminuria	0.0436	Sheffield diabetes model [68]
Healthy to Macroalbuminuria	0.0037	
Healthy to ESRD	0.0008	
Microalbuminuria to macroalbuminuria	0.1565	
Microalbuminuria to ESRD	0.0515	
Macroalbuminuria to ESRD	0.4335	
ESRD to death	0.0884	
Macroalbuminuria to death from ESRD	0.007	
Microalbuminuria to death from ESRD	0.0004	
ESRD to Transplant, 18-34 age	0.152	NICE TA358 [79]
ESRD to Transplant, 35-44 age	0.135	
ESRD to Transplant, 45-54 age	0.114	
ESRD to Transplant, 55-64 age	0.075	
ESRD to Transplant, 65+ age	0.039	
HbA1c adjustment β-coefficient for microalbuminuria	3.25	Sheffield diabetes model, see section 12.2.1 of the CS for how coefficients are used in model.[1, 68]
HbA1c adjustment β-coefficient for macroalbuminuria	7.95	
Early-onset type 2 diabetes relative risk of renal failure compared to type 1 diabetes	4.03	Dart et al. [81]
Transplant to Post-transplant	1	Assumption
Pancreatitis sub-model – Transition probabilities (unless stated otherwise), per cycle		

Parameters	Transition probability	Source
Odds ratio	0.93	ITC analysis (see Section 9.8)
Average events per year (untreated)	0.0261	Calculation
Average events per year (treated)	0.0071	Calculation
Neuropathy sub-model – Transition probabilities (unless stated otherwise), per cycle		
Healthy to clinically confirmed neuropathy	0.0512	Sheffield diabetes model [68]
Healthy to pad with amputation	0.0004	
Clinically confirmed neuropathy to pad with amputation	0.0225	
B-coefficient for neuropathy	5.30	Sheffield diabetes model, see section 12.2.1 of the CS for how coefficients are used in model.[1, 68]
OR for neuropathy complications adjustment for early-onset type 2 diabetes compared to type 1 diabetes	1.47	Song *et al.* [75]
Retinopathy sub-model – Transition probabilities (unless stated otherwise), per cycle		
Healthy to Background retinopathy	0.0454	Sheffield diabetes model [68]
Healthy to Proliferative retinopathy	0.0013	
Healthy to Macular oedema	0.0012	
Healthy to Blindness	0.0000019	
Background retinopathy to Proliferative retinopathy	0.0595	
Background retinopathy to Macular oedema	0.0512	
Background retinopathy to Blindness	0.0001	
Proliferative retinopathy to Blindness	0.0038	
Macular oedema to Blindness	0.0016	
β coefficient for Background retinopathy	10.10	Sheffield diabetes model [68], see section 12.2.1 of the CS for how coefficients are used in model.
β coefficient for Proliferative retinopathy	6.30	
β coefficient for Macular oedema	1.20	

Source: Table 42 in the CS.[1]
CS = company submission; CVD = cardiovascular disease; CHF = congestive heart failure; ESRD = end stage renal disease; HbA1c = glycosylated haemoglobin type A1c; GL = generalised lipodystrophy; ITC = indirect treatment comparison; MI = myocardial infarction; OR = odds ratio; PAD = peripheral arterial disease; PL = partial lipodystrophy.

The transition probabilities for the kidney, neuropathy and retinopathy sub-models were based on the approaches used in the Sheffield Diabetes model.[68] The cardiovascular baseline probabilities were derived from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.[73] Data from the Sheffield Diabetes model and DCCT/EDIC study was applied to determine the type of cardiovascular event (i.e. angina, MI, stroke or heart failure) and are summarised in Table 5.7 below. The probabilities of transitioning to the MI, CHF or stroke health states from angina were assumed to be the same as the probability of transitioning to each of the respective health states from the no CVD state. The remaining transition probabilities for the CVD sub-model were sourced from Smith *et al.*[70]

Table 5.7 Probability of different cardiovascular events

Cardiovascular event type	Probability of cardiovascular event	Source
MI	0.53	DCCT / EDIC; Sheffield Diabetes model. [68]
Stroke	0.07	
Angina	0.28	
Heart failure	0.12	
Source: Table 40 in the CS.[1] DCCT = Diabetes Control and Complications Trial; EDIC = epidemiology of diabetes interventions and complications; MI = myocardial infarction.		

In order to reflect the lipodystrophy population, the cardiovascular, kidney disease, neuropathy and retinopathy transition probabilities have been adjusted. This has been done in two ways. Firstly, adjusting the kidney, neuropathy and retinopathy transition probabilities to reflect the baseline HbA1c levels observed in lipodystrophy patients.

The transition probabilities for the kidney, neuropathy and retinopathy from the Sheffield Diabetes model were estimated at a reference HbA1c of 10%. The Eastman's method [84] has been used to adjust relevant transition probabilities to reflect a lipodystrophy patient's baseline HbA1c level using the formula shown below:

$$P_{HbA1c} = P_{HbA1c=10}(HbA1c/10)\text{^}\beta$$

The baseline probabilities $P_{HbA1c=10}$ were reported in the Sheffield diabetes paper. The equation above adjusts the risk of background retinopathy (10.10), macular oedema (1.20), proliferative retinopathy (6.30), microalbuminuria (3.25), macroalbuminuria (7.95), and neuropathy (5.30) using the β coefficients reported (shown in brackets).[68]

The second, adjustment is to reflect the risk associated with early-onset type 2 diabetes, which UK clinical experts validated as the closest form of diabetes observed in lipodystrophy patients.[1] The Sheffield diabetes model is for patients with type 1 diabetes. The baseline transition probabilities were therefore adjusted using risk ratios, which were converted from odds ratios, where appropriate, for organ-specific complications derived from literature for type 1 versus early-onset type 2 diabetes.[75, 76, 81] Song has shown that there is a statistically increased risk of cardiovascular and neuropathy events in early-onset type 2 diabetes compared to type 1 diabetes. As such, the odds ratios of 2.04 (p=0.04) and 1.47 (p=0.028) for cardiovascular and neuropathy, respectively, have been applied in the model to reflect the increased risk for lipodystrophy patients.[75] For the kidney sub-model transition probabilities, a risk adjustment was only applied to transition probabilities for end-stage renal failure, as estimates for

the relative risk between type 1 vs early-onset type 2 diabetes could not be sourced from literature for the remaining kidney sub-model health states.[81]

To overcome the limited lipodystrophy-specific data available for liver complications, the baseline transitions were utilised from the NICE NAFLD guideline, NG49.[66] The baseline rate of pancreatitis was directly sourced from the GL/PL natural history study (see section 9.8 of the CS for further details).[1]

Given that the risk of death was run separate to each of the sub-models, the transition probabilities for the sub-model health states from which patients have a probability of dying were reweighted by dividing by the complement of the probability of mortality for that particular health state.[1]

ERG comment: The transition probabilities for the six sub-models are based on published literature for diabetes. HbA1c is used as surrogate outcome to predict transition probabilities in the cardiovascular, kidney, neuropathy and retinopathy sub-models. Elevated triglycerides are known factors for cardiovascular complications. However, the company did not adjust the transition probabilities based on triglycerides due to lack of data in the literature. As such, the current transition probabilities are expected to be an underestimate where hypertriglyceridemia contributes to the risk of a complication, such as cardiovascular disease.

The observed reduction in HbA1c at 12 months is used to adjust the transition probabilities of patients taking metreleptin in the cardiovascular, kidney, neuropathy and retinopathy sub-models. As previously described the reduction in HbA1c due to metreleptin is modelled upon treatment initiation in the first cycle. Thereafter, all patients see an annual rise in HbA1c of 0.15%, up to a ceiling of 12% HbA1c, regardless of treatment group or treatment status (discontinued or not). This means that in the four sub-models using HbA1c to determine transition probabilities, there is no impact on the efficacy of metreleptin when patients discontinue, as they have already received the full benefit of metreleptin in terms of the reduction in HbA1c and their HbA1c rises at the same rate as patients taking metreleptin or under SoC from that point on. Therefore, post-discontinuation, the model assumes that the relative efficacy of metreleptin remains constant, over the lifetime, until patients in the SoC group reach the HbA1c ceiling of 12%, at which point the relative efficacy of metreleptin wanes, until these patients also reach the ceiling. Given the mean baseline HbA1c levels, the reduction in HbA1c due to metreleptin and the small annual rise in HbA1c, the average patient takes many years to reach the ceiling in either treatment group, as shown below in Table 5.8 and therefore this assumption of continued post-discontinuation efficacy has a large impact on results. The company provided no evidence on HbA1c levels post discontinuation from metreleptin as in the data cited by the company to justify this assumption of long-term efficacy (shown in Figure 5.10 and Figure 5.11), patients are still taking metreleptin.

Table 5.8 Implied relative efficacy of metreleptin versus SC on HbA1c

Patient group and treatment arm	Mean baseline HbA1c	Mean reduction in HbA1c	Mean cycle 1 HbA1C	Years to 12% ceiling	Implied relative efficacy
GL female SoC	8.8	0	8.8	21.33	21.33 years constant and 14.67 years waning
GL female metreleptin	8.8	-2.2	6.6	36	
GL male SoC	8.1	0	8.1	26	26 years constant and 14.67 years waning
GL male metreleptin	8.1	-2.2	5.9	40.67	
PL female SoC	8.8	0	8.8	21.33	

PL female metreleptin	8.8	-0.9	7.9	27.33	21.33 years constant and 6 years waning
PL male SoC	8.8	0	8.8	21.33	21.33 years constant and 6 years waning
PL male metreleptin	8.8	-0.9	7.9	27.33	
Based on: Electronic model company GL = generalised lipodystrophy; HbA1c = glycosylated haemoglobin type A1c; PL = partial lipodystrophy; SoC = standard of care.					

Also, from a logical standpoint, if there is no impact on efficacy after treatment discontinuation, the full benefit of a treatment is observed upon treatment initiation and thereafter patients HbA1c levels behave exactly the same as individuals not receiving treatment. Therefore, there is no incentive to provide more than one cycle of treatment as there is no additional benefit to be gained. This does not make sense in this case as it does not align with the necessary continued use of metreleptin over patients' lifetime.

The ERG looked further into the diabetes appraisal TA315 from where the assumed 0.15% annual increase in HbA1c was taken. This appraisal also modelled the full reduction in HbA1c due to treatment upon treatment initiation and then applied an annual increase in HbA1c across all patients. However, upon treatment discontinuation the company modelled a reversal in the treatment related reduction in HbA1c, as they did not have evidence of continued benefit after discontinuation.[88] The ERG feels that this method would be more appropriate as the company has no evidence of efficacy post-discontinuation and the way that HbA1c is currently modelled suggests no benefit in terms of organ complications of continuing treatment with metreleptin over the long-term, as the full benefit is received upon initiation. Thus, in Section 6 an alternative base case will be presented where upon treatment discontinuation a reversal in the treatment related reduction in HbA1c is modelled, in line with TA315.[88]

The liver sub-model uses the Delphi panel data for the metreleptin effect on the reduction of risk on liver complications. The ERG is concerned about the use of expert opinion for such values as relative efficacy is hard to judge on opinion. Given the availability of surrogate data on the reduction in AST/ALT from the ITC, the ERG would prefer to use this data in the base-case.

The ERG has a major concern regarding the use of the parameters from the ITC in the pancreas sub-model, for reason reported in section 4.6. The ERG has minor concerns related to each sub-model as described below.

Pancreas sub-model

The estimates of pancreatitis per year are not clear. The calculation is based on 230 patients from the Natural history study.[22] However, in the model the number of events of pancreatitis are reported as 45 whilst Akinci *et al.*[22] reports 30 events. The ERG corrected this value in the base-case and the results are shown in section 6.3.

Liver sub-model

In the model, the transition probability from asymptomatic liver disease to death is assumed to be zero. However, according to Younossi et al [66] (from where this transition probability was reported to be obtained), the six-month transition probability from F012 to death is 0.027. The reason for the discrepancy between the source the company refers to and the input of the model is not explained or justified by the company. Given that all patients are assumed to start in the asymptomatic health state (F012), changing the probability of death from 0 to 0.027 is likely to have a large impact on the outcomes of the model. However, the ERG observed that the probability from F3 to death and from

compensated cirrhosis to death are 0.003 and 0.011, respectively, suggesting that the 0.027 probability to die for patients in F012 might be a gross over-estimation.

In addition, the assumption that all patients who start metreleptin have asymptomatic liver disease is questionable. The company states in section 9.4.3 of the CS:

"In NIH studies 991265/200110769 all 107 patients had at least one medical history event reported. The most commonly reported medical history events in GL patients were hypertriglyceridaemia (71%) and diabetes mellitus (70%). Other relevant medical history included hepatomegaly/ hepatosplenomegaly (62%), NASH including steatohepatitis (52%), proteinuria (45%), hypertension (36%), insulin resistance (29%), pancreatitis (27%), hepatic steatosis (24%) and hirsutism (21%).

Of the defined PL subgroup, 94% of these patients had a history of hypertriglyceridaemia and 84% had diabetes. Hepatic steatosis and pancreatitis were each reported in 39% of PL subgroup patients, 23% had polycystic ovaries and 26% had NASH including steatohepatitis." [1]

However, it was not possible based on the data provided to link previous events to a certain level of liver fibrosis.

The company provided a scenario analysis for the liver model where ALT and AST are used to calculate the probability of advanced fibrosis (PAF) according to the formula reported in Hossain *et al.* [72] reported below:

$$PAF = -0.1696 + 0.0964 \times male + 0.1170 \times Caucasian + 0.1065 \times diabetes\ mellitus + 0.0039 \times ALT + 0.0130 \times AST$$

The company set the value of the coefficient for the Caucasian to zero as it is assumed that ethnicity has no effect on the outcomes, as reported in section 17.12.1 of the CS and reiterated in the answer to question A35 and B35.[37]

Cardiovascular sub-model

The transition probabilities based on the publication by Smith *et al.*[70] are calculated using risk estimates based on the Framingham Heart Study and a cohort study conducted in Canada between 2003 and 2005.[90-92] The estimates are therefore based on subjects who developed myocardial infarction (MI), congestive heart failure (CHF) and stroke derived from general population (not UK specific), not necessarily hyperglycaemic. This data is also not very recent. These limitations in the data could cause some potential bias.

Kidney sub-model

The company used the hazard ratio (HR) for risk of renal failure reported in Dart *et al.*[81] The company treated it as an odds ratio (OR) and convert it to probability. The ERG corrected this estimation in the base-case scenario presented in section 6.3 using the following conversion:[93]

$$RR = \frac{1 - e^{HR \times ln\,(1-r)}}{r}$$

where RR is the relative risk, *r* is the baseline probability rate for the reference group.

5.3.3.4 Mortality

In order to avoid double counting mortality in each Markov sub-model, the risk of mortality runs separately alongside the various sub-models.[1] All-cause mortality was sourced from UK Life tables available from the Office for National Statistics.[86] Risk of mortality is assumed to not fall below that of

the UK national life tables as it is assumed that a patient with no complications would have a similar risk of death to that of the general population – i.e. a patient's excess mortality risk is primarily driven by the risk of death associated with the various complications they experience at a particular time point.

States which would inflate the risk of mortality past that of all-cause mortality, and the risk inflation attached to these states, are presented in the CS in Table 41.[1] These mortality risk inflators from the separate models are then aggregated using a conservative approach (selecting the highest individual risk of death across all organ systems) to create a single probability for mortality risk. Patients then have a random chance of dying from this mortality risk in any cycle. For a cycle in which a patient dies, the effect of costs and QALYs are reduced by half and reduced to zero from the subsequent cycle onwards.[1]

ERG comment: The ERG agrees on the company's approach as no mortality benefit for metreleptin has been shown by the ITC (HR=1.38 [95%CI: 1.88; 20.37], P-value=0.42, Table 33 in the CS[1]). It should be noted though that the confidence interval reported in the CS does not contain 1, and neither does it contain the HR, so the ERG assumes that it contains a typo.

5.3.3.5 Adverse events

Adverse events were not included in the cost effectiveness analysis.[1] The impact of adverse events on costs and utilities were anticipated by the company to have minimal impact on costs as they were mild or moderate in their severity and occurred at a low frequency. The impact of the organ system complications included in the sub-models are accounted for in the costs and utilities in the economic model.

ERG comment: The ERG would have preferred that Grade 3+ treatment-emergent adverse events (TEAEs) were included in the model for completeness as it is not possible to judge their impact without first including them. However, the ERG agrees that they are unlikely to be the driver of cost effectiveness.

5.3.3.6 Discontinuation

The annual discontinuation rate for treatment non-compliance from NIH studies 991265/200110769 (1.50% for patients with GL and 3.86% for patients with PL) were employed in the model.[1] Discontinuations due to all reasons observed in the NIH studies 991265/200110769 were not considered to represent that expected to be observed in clinical practice because a number of patients discontinued the studies prematurely to enter the Early Access Programme for metreleptin initiated in the US prior to FDA approval.

ERG comment: The ERG did not agree with the company choice that only discontinuation due to non-compliance should be included in the modelled discontinuation. The ERG asked the company to provide the annual discontinuation rate due to all reasons for GL and PL patients separately and to clarify how many patients discontinued the NIH studies 991265/200110769 studies to enter the Early Access Programme. In response to question B8 part 2 of the clarification letter,[37] the company reported that the annual discontinuation rates due to all reasons in the NIH studies were 7.91% and 10.76% for GL and PL patients, respectively. From the 23 GL patients who discontinued treatment prematurely, eight of these patients discontinued to transfer to EAPs. From the 15 PL patients who discontinued prematurely, two of these patients discontinued to transfer to EAPs. In their scenario analyses in Part 2 of the clarification response, the company also provided time-based Final Evaluation Decision (FED) discontinuation rates of 8.93% in the first year, 5.63% in years 2 to 9, and 2.04% for year 10 and over. Given that these provide long-term estimates of discontinuation and show a plausible trend in discontinuation, with larger discontinuation in the first years, followed by lower discontinuation in the

long-term, the ERG prefers to use these estimates in their base-case. The ERG ran a scenario analysis using the three available sets of discontinuation rates and the results are shown in section 6.4.

The ERG has also concerns about assumptions made regarding the long-term effect of metreleptin. The ERG asked the company to clarify: for how long the model assumes the partial treatment effect post discontinuation; the size of the continued treatment effect assumed for these clinical outcomes and; how these assumptions are justified by the long-term data quoted in the CS.[37] Additionally, the ERG asked the company to provide the option in the model to use the durations of 48 and 36 months for the continued treatment effect for GL and PL patients respectively, accounting for the proportion of treatment effect which remains over time (question B9 part 2 CL[37]).

The company replied: "In patients receiving metreleptin, HbA1c reductions occur as a one-off event at the start of treatment (model start); this decrease does not occur in patients receiving SC alone. From this point, HbA1c begins to rise on an annual basis at the same rate in patients who remain on treatment and who discontinue, as well as those treated with SC alone. This annual rise continues up to a ceiling value of 12%, based on clinical opinion from the Delphi Panel. As such, there is a 'lag' effect on HbA1c with treatment (i.e. a treated patient starts from a lower HbA1c value than if they did not receive treatment); we feel it would be unrealistic to reverse the reduction at a specific point (i.e. to model a 'jump' in HbA1c), given all patients' HbA1c levels rise to the same ceiling point over time.

Liver benefits are maintained post discontinuation under the assumption that a short-term reduction in fatty deposits and accumulation in the liver will yield a longer-term benefit – creating a similarly "lagged" effect and slowing the progression to later stages of disease.

Furthermore, it should be noted that clinical improvements seen in NIH studies 991265/200110769 (and subsequent ITC) upon which the model is based are inclusive of discontinued patients, suggesting any impact this has on the overall benefit of metreleptin has already been factored into the values used.

The company included an option in the model to remove the effect of liver benefits after 36 and 48 months.

5.3.3.7 Health-related quality of life

Impact of lipodystrophy on HRQoL

Lipodystrophy is a progressive, chronic disease, which results in a complex range of complications developing over multiple organs.[1] Patients with lipodystrophy suffer from a range of health issues which can impact their HRQoL including: hyperphagia, poor metabolic control, ectopic fat accumulation in organs, insulin resistance, diabetes and hypertriglyceridaemia, a variety of liver abnormalities such as hepatic steatosis, renal complication associated with dialysis and transplant. As a result of such metabolic complications patients may develop several chronic complications which have a substantial effect on both quality of life and mortality such as pancreatitis, renal failure, and cardiovascular disease. Patients can also experience psychological disturbances such as anxiety, depression and fatigue, with depressive symptoms often compounded due to the impaired physical appearance associated with lipodystrophy, leading to low self-esteem.[1]

HRQoL declines progressively in lipodystrophy patients as the metabolic disease and organ damage worsen over time with disease progression. The rapid progression of organ damage has a significant impact on QoL, with the associated utility decrement in the year before metreleptin administration estimated to be -0.162 over time.[63]

GL patients are affected from birth or very early childhood. GL patients experience a variety of symptoms as a consequence of a lack of adipose tissue, including hypertriglyceridaemia, hyperphagia as a result of underlying leptin deficiency, acromegaloid features and hyperinsulinemia at a young age.[5] This results in a vastly reduced quality of life from early childhood, which is likely to continue into adulthood. PL patients may have a relatively normal body fat distribution until around puberty. Metabolic abnormalities arise in early adulthood in PL patients and ultimately result in many of the lipodystrophy-associated complications, such as a variable lack of adipose tissue leading to hypertriglyceridaemia, pancreatitis and cardiomyopathies.[5] Acquired forms of lipodystrophy tend to present with a progressive lack of fat tissue in childhood or adolescence, leading to a progressive deterioration in HRQoL. Acquired forms of lipodystrophy have also been associated with later development of autoimmune disease such as rheumatoid arthritis and Crohn's disease.[94-96]

HRQoL evidence

No HRQoL data were collected in the clinical trials led by NIH identified in the company submission. Therefore, the company conducted a SLR to identify sources of utility values from the literature. Details of the HRQoL SLR conducted are provided in Section 5.2 of this report. The SLRs conducted for the previous metreleptin submission originally identified two HRQoL references for data extraction. The updated SLR identified one additional study.

One published abstract reporting HRQoL data for lipodystrophy patients was identified in the SLR. In this study by Ali et al. the HRQoL of GL and PL patients was valued using a discrete choice experiment (DCE) with 1,000 members of the general population from the US, UK, France, Germany, Italy and Spain to assess the QALY gains associated with metreleptin.[63] This study was also utilised in the previous metreleptin submission.[62] The survey consisted of three sections: a demographic questionnaire, a tutorial informing respondents about the disease and its associated attributes and the DCE exercise.[1, 97] Multinomial logit regression was used to estimate utility decrements associated with different QoL attributes including impaired work/school ability, hyperphagia and organ damage. Resulting decrements were combined with data on the prevalence of attributes before and after one year of metreleptin therapy in 114 lipodystrophy patients, of which 61% were GL and 39% PL, to assess overall QoL consequences, and the impact of metreleptin on QALYs.[1, 63] Results indicated that lipodystrophy has a large impact on utility and that metreleptin was associated with a QALY gain of 0.423 across all patients. Considering the GL and PL subgroups separately resulted in QALY gains of 0.569 and 0.199 respectively.[63]

Impact of adverse events on HRQoL

In the submission the company reported that the most common drug-related treatment emergent adverse events (TEAEs) in the NIH 991265/20010769 and FHA101 studies were mild to moderate in severity and that most severe TEAEs were consistent with known symptoms or complications of lipodystrophy (e.g. renal failure, cardiac arrest and pancreatitis), and were not considered to be drug related. The company identified hypoglycaemia as the only key drug-related complication. As metreleptin lowers the effect of insulin resistance in patients with lipodystrophy with diabetes, there is an increasing risk of hypoglycaemia as doses are titrated. However, this was assumed to have a minimal impact on HRQoL given the short duration of symptoms and was therefore not included in the model.

Utility values used in the cost effectiveness analysis

Given the wide ranging comorbidities relating to organ complications included in the more than 30 model health states, where possible the company reported that they used health state utility values from

cohorts with combined health conditions, as advised by the Decision Support Unit TSD 12.[98] Therefore, where possible, the company used utility values from the UKPDS 62 sub-study by Clarke *et al.,* where patients with type 2 diabetes were followed up for 30 years and experienced multiple complications across multiple organs covering a number of diabetes-related health states.[99] This population was assumed generalisable to lipodystrophy patients, given that lipodystrophy leads to insulin-resistant diabetes, and this is therefore a common characteristic in lipodystrophy patients.

In the UKPDS 62, HRQoL was measured in 3,667 UKPDS patients with type 2 diabetes using the EQ-5D to estimate the impact of diabetes-related complications on utility over a follow up period of 30 years.[99] This source of utility values has been widely used and accepted in multiple NICE appraisals in type 2 diabetes, e.g. TA288, TA336 and TA390.[100-102] Likelihood ratio tests were performed on relevant utility values obtained from the UKPDS study to determine whether a significant difference existed between the coefficients for the disutility if the event occurred within the previous year or more than one year ago. In all cases the difference between these coefficients were insignificant and therefore the same disutility values were applied in the event year and post event-year based on the assumption that the effect of compilations on utility does not vary over time.[1]

For the liver sub-model, utility values were estimated from the NICE NAFLD guideline.[66] Utility decrements for each health state were calculated by deducting the utility value for each health state from the utility value for the 'NAFL-NASH (F012) – treated' health state. The utility decrements for compensated cirrhosis with varices and decompensated cirrhosis with varices health states were assumed to be the same as the utility decrements for the compensated cirrhosis and decompensated cirrhosis health states respectively.[1]

The utility value for acute pancreatitis was obtained from the previous metreleptin submission.[97] as the company did not identify any suitable alternatives in the literature. The utility decrement for acute pancreatitis of 0.13 used in the model was estimated from the DCE previously described.[62]

Utility values for other organ sub-models were described as obtained from other published sources and those previously used and accepted in relevant NICE appraisals. Sources were provided in Table 35 of the CS but no further details were given.[1]

The CS also describes a number of symptoms of lipodystrophy that significantly impact patient QoL, including hyperphagia, dysmorphia PCOS and female reproductive dysfunction, which were assumed not to be captured by the organ specific sub-models.[1] To account for such complications, a disutility of 0.13, drawn from the previous metreleptin submission for hyperphagia alone, was applied to patients treated with SoC alone.[1, 97] The company stated that this value was also estimated from the DCE study previously described. While they acknowledge the limitations associated with the DCE they stated that no alternative value could be sourced from the literature.

The model also included a utility decrement associated to the burden on caregivers of -0.0986. This decrement was estimated as the difference between the mean (SE) EQ-5D TTO value for caregivers 0.8124 (0.043), taken from the Lipodystrophy Caregiver Burden Survey and the general population norm, obtained from the EQ-5D UK-specific TTO value for the relevant age group (mean age of carers in the Lipodystrophy Caregiver Burden Survey was 43.7) of 0.893.[1, 29, 103, 104] It was assumed that each patient had two carers who would experience this burden of care, based on data from the Lipodystrophy Caregiver Burden Survey, which showed that on average patients had 1.67 carers, which was rounded to two carers on average by the company.[29, 37]

Relevant utility decrements associated with model health states and events were subtracted from age-dependent baseline utility values which were assumed equal to UK general population norms.[103, 104] It was assumed that these UK population would be representative of a lipodystrophy patient without any symptoms, who would be expected to have a relatively unaffected QoL.[1] For patients experiencing multiple complications across the different organ sub-models, the decrements associated with each organ are applied to the baseline value using a multiplicative approach creating a single proportional decrement relative to baseline utility, as recommended in NICE TSD12.[98]

A summary of all utility values and disutilities included in the model is provided below in Table 5.9.

Table 5.9 Utility values used in the model

Parameter	Base-case value	Source	Justification
Treatment based utility values			
Metreleptin	0.81	Unclear – difference between these values is based on the decrement for hyperphagia from the DCE, but unclear where initial value of 0.81 came from. However this 0.81 is not used directly in the model – only the differential of 0.12 is used	Organ models do not pick up treatment related benefits to QoL such as reduction on hyperphagia and PCOS and improved physical appearance and ability to perform work/school work
SoC	0.69		
Liver sub-model utility decrements			
Asymptomatic liver disease	-0.03	NAFL-NASH (F012) utility from NAFLD NICE guideline.[66]	Consistency with NAFLD NICE guideline
Advanced fibrosis	-0.15	Fibrosis F3 utility from NAFLD NICE guideline [66]	
Compensated cirrhosis	-0.27	NAFLD NICE guideline [66]	
Decompensated cirrhosis	-0.33		
Compensated cirrhosis with varices	-0.27		
Decompensated cirrhosis with varices	-0.33		
Variceal bleeding	-0.33		
Hepatocellular carcinoma	-0.33		
Liver transplant	-0.07		
Post liver transplant	-0.02		

Parameter	Base-case value	Source	Justification
CVD sub-model utility decrements			
Angina	-0.09	NICE TA288, TA366, TA390;[100-102] Clarke *et al.* (UKPDS)[99, 100]	EQ5D, UK sample and value set
Stroke	-0.164		
Congestive heart failure	-0.108		
Myocardial infarction	-0.055		
Kidney sub-model utility decrements			
Microalbuminuria	0	NICE NG17[105]	Conservative estimate, consistent with NICE NG17
Macroalbuminuria	-0.048	Beaudet *et al.* [106]	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case. The disutility applied was assumed to equal the disutility for proteinuria (consistent with costing approach for macroalbuminuria).
End stage renal disease	-0.222	NICE TA358; Lee *et al.* [107]	EQ-5D, UK sample and value set
Kidney transplant (year 1)	-0.148	NICE TA358; Clinical opinion [79]	Consistency with NICE TA358 submission, from which the utility value for the post-kidney transplant (year 2+) value was sourced.
Post kidney transplant (year 2+)	-0.082	NICE TA358; Lee *et al.* [79, 107]	EQ-5D, UK sample and value set
Pancreatitis sub-model utility decrements			
Acute pancreatitis	-0.13	NICE ID861 [97]	Suitable value not available from literature
Retinopathy sub-model utility decrements			
Background retinopathy	-0.027	NICE TA597; Peasgood *et al.* [108, 109]	EQ5D, UK sample and value set
Proliferative retinopathy	-0.07	NICE TA597; Beaudet *et al.* [106, 109]	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case
Macular oedema	-0.04	NICE TA597; Beaudet *et al.* [106, 109]	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case
Blindness	-0.074	NICE TA597; Clarke *et al.* (UKPDS)[99, 109]	EQ5D, UK sample and value set
Neuropathy sub-model utility decrements			

Parameter	Base-case value	Source	Justification
Peripheral neuropathy	-0.084	NICE TA597; Beaudet *et al.* [106, 109]	Preferred utility value from Beaudet *et al.* SLR, based on consistency with the NICE reference case
Amputation	-0.28	NICE TA288, TA366, TA390;[100-102] Clarke *et al.* (UKPDS)[99, 100]	EQ5D, UK sample and value set
Caregiver burden decrement			
Caregiver burden	-0.0986	Janssen *et al.*; Kind *et al.* Caregiver Burden Survey[29, 103, 104]	Inclusion of caregiver disutility has been accepted in previous NICE HST submissions for similarly devastating diseases [110]
Age-specific general population values			
<18	0.94	Assumption	HRQoL declines with increasing age
18 – 24	0.94	Janssen *et al.*; Kind et al. [103, 104]	
25 – 34	0.927		
35 – 44	0.911		
45 – 54	0.847		
55 – 64	0.799		
65 – 74	0.779		
75+	0.726		

Source: Table 35 in the CS.[1]
CS = company submission; DCE = discrete choice experiment; HRQoL = health related quality of life; PCOS = polycystic ovary syndrome; SLR = systematic literature review; SoC = standard of care; QoL = quality of life

ERG comment: In general, the utility values used in the organ sub-models were traceable. However, given that these values were measured in different patient populations, it is unclear how generalisable these values are to lipodystrophy patients. However, given the data currently available and the model structure, this approach and the sources selected make sense.

Utility decrements associated with pancreatitis and the differential between patients on metreleptin treatment and those only receiving SoC were based on the DCE study presented in the original metreleptin submission.[62] This study was associated with many issues in the first appraisal process, which were extensively described in the original ERG report and subsequent submission of additional evidence by the company.[62, 111, 112] Briefly the issues included:

- In each choice task participants had to choose between two choice cards each containing 12 (out of 20) attributes, all of which varied simultaneously. This makes the task very complex.
- Task complexity was increased by the fact that some of the included attributes and their impact on health would not be well known to respondents (e.g. triglyceride blood fat control and impaired blood sugar control). Despite substantial information being provided to respondents prior to the choice survey, it is unlikely that they managed to retain all of this information and therefore their understanding of included attributes may have affected their ability to make informed choices and is likely to have affected results.

These issues increase the risk that participants will use heuristic shortcuts, such as always making a decision based on the same couple of attributes (likely life expectancy or age) or participants will simply rely on the colour coding and choose the situation with most green attributes.

- Age and life expectancy were both included in the choice tasks. Life expectancy (defined as age + remaining years of life) could be easily misinterpreted by respondents as simply remaining years of life.
- The age attribute levels covered adults and children simultaneously. However, decision making for adults and children are known to be subject to very different value judgements.
- Selection of attributes was not discussed with patients and therefore important aspects of the impact of lipodystrophy on HRQoL may have been missed, or irrelevant aspects included.
- Attributes were colour coded, with the intention of red for more severe outcomes and green for less severe. However, the colour coding was incorrectly fixed and therefore often highlighted attribute levels incorrectly and varied across attributes.
- The modelling was overly simplistic and did not account for the likelihood that some participants used heuristic shortcuts such as "always choose the card with the least impairments", or "always choose cards with more life remaining."
- The company treated all resulting model coefficients as utility decrements, subtracted from 1 (perfect health). However, this resulted in implausibly low utility values given the number of attributes and size of coefficients.

All of these issues mean that it is very difficult to place confidence in the results of the DCE study. In their second evidence submission, in November 2018, the company did attempt to resolve some of these issues.[111] The DCE data was reanalysed using an improved logistic model to estimate attribute coefficients which included dummy variables identifying choice cards with more impairments, and choice cards with more life remaining to address concerns that respondents may have used heuristic shortcuts to make choices, such as always choosing cards with fewer impairments, or always choosing cards with more life remaining.[111] The decrements obtained were also anchored to the EQ-5D-3L UK tariff so that the worst possible state was given a value of -0.594 to ensure that the resulting utility value would be plausible. However, the disutilities of 0.13 and 0.11 reportedly used in the current model for acute pancreatitis and hyperphagia respectively were obtained from the original DCE results, prior to this reanalysis, which is concerning. Following reanalysis and anchoring these disutilities were estimated to be 0.06 and 0.071 respectively.

The CS reported that a utility decrement of -0.13 was applied in the model to those patients receiving only SoC. This was intended to account for a number of aspects of lipodystrophy that significantly impact patient QoL, including hyperphagia, dysmorphia PCOS and female reproductive dysfunction which were assumed not to be captured by the organ specific sub-models. This decrement of -0.13 (which in the model was actually -0.12) was reported as drawn from the decrement for hyperphagia alone from the previous metreleptin submission. This original decrement was reported as calculated from the DCE study. However, the decrement for hyperphagia reported in the original ERG report was -0.11.[112] When the ERG queried this in clarification the company reported that the decrement of -0.12 was based on the decrement of -0.11 for hyperphagia from the original submission but a number of factors were considered when arriving at the final value, including:

- This decrement of -0.11 was later revised to -0.071 through reanalysis of the DCE as part of the previous submission materials.[111]

- This value may underestimate the impact of hyperphagia as the DCE cannot fully encompass the patient experience of such a unique aspect of the disease (e.g. members of the general public may not have understood how hyperphagia differs from usual "hunger").
- Bridges et al. estimated that hyperphagia is associated with a utility decrement of -0.13 and -0.09 when assessed using visual analogue scale (VAS) and time-trade off (TTO), respectively, among patients with Prader-Willi syndrome.[113]
- Further to hyperphagia, a number of symptoms associated with lipodystrophy, which metreleptin has been shown to improve, have not been captured in the organ sub-models. These symptoms include inability to perform work/schoolwork, disruption to female reproductive functioning (PCOS) and impaired physical appearance. The decrement of -0.12 also seeks to account for the reduction in the frequency or severity in these symptoms as a result of metreleptin treatment.[37]

In the re-analysis of the DCE, discussed above, the symptoms of metreleptin which the company assumed to be uncaptured by the current model were associated with the following rescaled decrements and prevalences displayed in Table 5.10. The ERG calculated expected disutilities for patients receiving metreleptin and SoC (assuming the prevalence for post treatment represented metreleptin and pre-treatment represented SoC) and assuming that 43.48% of patients were GL and 56.52% PL, as assumed in the company model. This resulted in an expected disutility of 0.174 for SoC patients and 0.057 for metreleptin patients, resulting in a treatment differential of 0.117. This is slightly smaller than the 0.12 treatment differential assumed in the model, but not vastly different.

Table 5.10 Rescaled DCE decrements and prevalence of symptoms and complications

Symptom/ complication	Rescaled decrement	Prevalence			
		GL Pre-treatment	PL Pre-treatment	GL Post-treatment	PL Post-treatment
inability to perform work/schoolwork	0.167	57.4%	20.5%	11.8%	9.1%
hyperphagia	0.071	82.3%	71.9%	11.3%	9.4%
PCOS	0.026	47.7%	77.4%	27.3%	64.5%
impaired physical appearance	0.056	82.4%	68.2%	29.4%	40.9%

Source: ID861 ECD additional evidence v0.1 2018.[111]
GL = generalised lipodystrophy; PCOS = polycystic ovary syndrome; PL = partial lipodystrophy

However, this does not mean that we can have confidence that the resulting disutility for SoC is representative of the true difference between patients receiving and not receiving metreleptin. The estimated disutility is still based on a DCE, where the many design issues make it difficult to have confidence in either the reanalysed or original coefficients. Additionally, we cannot be sure that the symptoms of metreleptin assumed by the company to not be covered by the organ model (hyperphagia, inability to perform work/schoolwork, PCOS and impaired physical appearance) are not already somewhat covered in the decrements within the organ models (particularly inability to work). We also cannot be sure that this list fully covers the issues which impact the QoL of lipodystrophy patients outside of the organ model. Given the extensive uncertainties in terms of HRQoL, both regarding the generalisability of utility decrements from other populations and limitations in the study design of the lipodystrophy DCE study, the ERG feel that no changes to the utility values or decrements assumed for patients can be made by the ERG in the base-case as no better alternatives are available.

Several issues arose surrounding the assumptions made about the disutility of caring for patients with metreleptin. Firstly, the company submission reported that the disutility of 0.0986 associated with caring was estimated as the difference between the mean EQ-5D utility from the Lipodystrophy Caregiver Burden Survey and the general population norm, obtained from the EQ-5D UK-specific TTO value for individuals aged 43.7, reflecting the mean age of carers in the survey.[29] However, no mean EQ-5D value for carers from the Lipodystrophy Caregiver Burden Survey was provided with the submission. This was requested at clarification and reported to be 0.8124 (SE 0.043). The UK EQ-5D general population norm at the age of 43.7 is 0.911, which corresponds with the company base-case disutility of 0.0986. However, the company use a different set of EQ-5D general population norms (the UK-England values) from the same publication by Janssen et al. in the rest of the model. The UK-England values are used by the company as age-adjusted baseline utilities from which all utility decrements are subtracted. In order to maintain consistency with the rest of the model, the ERG prefer to use the UK-England EQ-5D general population norm at the age of 43.7 of 0.893 in the calculation of the disutility due to caring in the ERG base-case.[103, 104] This corresponds to a disutility due to caring of 0.0806 in the ERG base-case.

In addition, the company base-case assumed that each patient had two carers, which they justified as the mean number of carers per patient in the Lipodystrophy Caregiver Burden Survey in the CS.[29] However, the ERG noted that the true mean value from the Lipodystrophy Caregiver Burden Survey data was 1.67 and that the model contained three alternative assumptions for the number of carers; single carer, multi carer and average carer. Reasonably, the single carer scenario assumed one carer per patient and the multi carer scenario two per patient. However, the average carer scenario also assumed two carers per patient despite the true average being 1.67. This was queried by the ERG in the clarification letter. The company responded that despite the mean number of carers being 1.67, the average carer scenario used a rounded value of two as it is most representative of the most common scenario in practice.[37] However, rounding up the mean overestimates the number of carers. This was corrected in the company model and the ERG base-case uses the average value of 1.67.

The final issue is that the company assumed that those patients who discontinued from metreleptin continued to receive 50% of the treatment benefit in terms of utility differential between metreleptin and SoC over the rest of their lifetime. A 50% maintained treatment effect was also assumed for carers over the same lifetime duration. When the ERG asked for evidence justifying this assumption in the clarification letter the company responded that this assumption was implemented as a way of capturing a number of factors.[37] The first factor was to reflect the "lag" in treatment effect on HbA1c, and the longer-term benefits this will entail. Furthermore the company stated that, while not captured via the organ-specific models except for its inclusion as part of the stopping rule, the ITC demonstrated a clinically significant reduction in triglyceride levels amongst metreleptin-treated patients; this would also be expected to contribute to the initial and subsequent sustained effect, and the same lag as with HbA1c would be expected, assuming it were modelled in a similar way. The experts forming the Delphi Panel all agreed that triglycerides contribute to the development of cardiovascular complications in lipodystrophy patients. Therefore, treatment with metreleptin also further reduces the risk of cardiovascular and other complications in a way not captured in the model for reasons of conservatism (to avoid 'doubling' cardiovascular effects by using both markers). As such, even after discontinuation, the company felt it was reasonable to expect that a patient would, to some extent maintain some cardiovascular and other treatment related benefit with respect to triglyceride reduction. Furthermore, they noted that clinical improvements seen in NIH studies 991265/200110769 (9) (and subsequent ITC) upon which the model is based are inclusive of discontinued patients, suggesting any impact this has on the overall benefit of metreleptin is already factored into the values used.[37]

The ERG has several concerns about this justification. The arguments mentioned are all based on HbA1c and triglycerides. HbA1c controls the probability of organ complications in the sub-models. Benefits of delaying or preventing organ complications are already translated into utility benefits for patients through delayed or prevented utility decrements associated with organ complications in these sub-models. However, the 50% of utility benefit maintained for patients over their lifetime in the model is associated with a lower incidence of the symptoms of hyperphagia, inability to work, PCOS and impaired physical appearance in patients taking metreleptin. No evidence has been provided that these issues are reduced once a patient discontinues from metreleptin compared to patients who only received SoC. The 50% utility benefit to carers is based on the difference between the EQ-5D utilities estimated from carers responses to the EQ-5D and the mean general population utility in the UK. Here there could be an argument that if there are indeed lagged and continued benefits associated with metreleptin treatment after discontinuation in any area of the model, these benefits could be felt by carers after the patient discontinues. However, given that the company provided no evidence of continued treatment effect after discontinuation, this assumption was also not justified. Therefore, the assumption of 50% continued lifetime treatment effect over for patients and carers was removed in the ERG base-case.

5.3.3.8 Resources and costs

For the cost effectiveness model, the company included the following categories of costs: drug acquisition costs (metreleptin arm only), routine monitoring costs (both metreleptin and supportive care), supportive care costs (both metreleptin and supportive care), and the costs of lipodystrophy-related complications (both metreleptin and supportive care). The latter are applied in the health states of the various sub-models that relate to pancreatitis, liver disease, cardiovascular disease, kidney disease, and neuropathy and retinopathy. Drug administration costs for metreleptin, which would consist of the costs for home delivery and self-administration training, were not included since these costs will be funded by the company at no additional cost to patients or the NHS. The company did not provide an estimate of these costs, or an indication of the extent to which these costs affect the drug acquisition costs for metreleptin. All costs included in the analysis were inflated to 2018/2019 values using the NHS Cost Inflation Index (NHSCII) from Personal Social Services Research Unit 2019.[114]

Drug acquisition costs

Metreleptin is available in three vial sizes for injection for the following list prices per pack of 30 vials: 10 mg for £70,050, 5 mg for £35,025, and 2.5 mg for £17,512.50. A PAS discount of [redacted]% is applied to these list prices, which gives the following per vial cost prices that are applied in the model: £[redacted] per 10 mg vial, £[redacted] per 5 mg vial, and £[redacted] per 2.5 mg vial.

Metreleptin dosage assumptions are based on data from the Early Access Programme (EAP) at Addenbrooke's Hospital and corresponds to the proportions of patients receiving each dose that are shown in Table 5.11.

Table 5.11: Proportions of patients receiving each metreleptin vial size

	10 mg vial	5 mg vial	2.5 mg vial
Proportion of EAP patients receiving each vial size	13.0%	60.9%	26.1%

Source: Table 44 in CS.[1]
EAP = Early Access Programme; mg = milligram

It is assumed that all patients initiate treatment with the 2.5 mg vial size. Dose titration is modelled to occur in a stepwise fashion (i.e. with patients who ultimately receive 10 mg from the third cycle onwards first receiving 5 mg in the second cycle) and applied to the proportions shown in Table 5.11 in the

subsequent model cycles. Hence, the first two cycles of the model are the dose titration phase, and from the third cycle onwards all patients receive their corresponding long-term dose until discontinuation of treatment. For patients with a body weight below 40 kg, a dosage of 0.06 * body weight is assumed (applied to a per mg price for metreleptin).

Routine monitoring costs

Based on a Delphi Panel of UK clinicians, it was assumed that 1 to 2 additional visits for routine monitoring are required in the first year for patients who receive treatment with metreleptin in comparison to patients who receive treatment only with supportive care. After the first year, the routine monitoring requirements are assumed the same for both treatments. A single routine monitoring visit is assumed to consist of a combination of a joint appointment with a dietician and a diabetic nurse, and an endocrinologist consultant. The unit costs for visits to each of these health professionals and the total cost for a routine monitoring visit are listed in Table 5.12. In the model, the costs of 2 additional routine monitoring visits are included for patients receiving metreleptin. This gives the annual costs for routine monitoring as shown in Table 5.13 for both treatments.

Table 5.12: Unit costs for each component and total costs of a routine monitoring visit

Appointment	Cost per visit	Source
Consultant endocrinologist outpatient appointment	£178.06	NHS reference costs 2017/2018, weighted average of service codes: 252 and 302 (consultant) inflated to 2018/2019 using the NHSCII from PSSRU 2019[114, 115]
Dietician outpatient appointment	£84.55	NHS reference costs 2017/2018, service code 654 (Total) inflated to 2018/2019 using the NHSCII[114, 115]
Diabetic nurse outpatient appointment	£62.85	NHS reference costs 2017/2018, weighted average of currency codes N15AF, N15AN, N1FCF and N15CN inflated to 2018/2019 using the NHSCII[114, 115]
Total cost for a routine monitoring visit	£325.46	-

Source: Table 45 in the CS.[1]
NHS = National Health Service; NHSCII = National Health Service Cost Inflation Index; PSSRU = Personal Social Services Research Unit.

Table 5.13: Annual costs for routine monitoring visits per treatment

Treatment	Annual routine monitoring costs	
	Year 1	Year 2 and onwards
Metreleptin	£976.38	£325.46
Supportive care only	£325.46	£325.46

Source: Table 46 in the CS.[1]

Supportive care medication costs

In addition to routine monitoring visits, the costs of supportive care are assumed to consist of various medications for the management of metabolic complications. Based on the NIH studies

991265/20010769,[52] the following medication classes were assumed for patients receiving supportive care only:

- Insulin (assumed to be intermediate or long acting insulin, combined with fast acting insulin in a 70:30 ratio).
- Oral antidiabetic medication: biguanides, thiazolidinediones and sulfonylureas.
- Lipid-lowering therapies: HMG CoA Reductase inhibitors and other lipid modifying agents.
- Other concomitant medications: lisinopril and enalapril.

Based on NHS prescription cost data,[116] the most commonly described medication was identified for each class of medication listed above, and their strength and form determined. The strength for each medication was assumed to be the daily dose for all supportive care medications except colesevelam, based on this daily dose falling within the range of doses as recommended in the BNF.[117] For colesevelam, the daily dose fell outside the range mentioned in the BNF, and therefore the lowest dose from the BNF was conservatively assumed. Details on the assumptions made for the calculation of medication costs for patients receiving supportive care only, as well as daily cohort costs, total cohort costs, and average per patient costs for each subgroup are provided in Table 5.14.

Table 5.14: Medication costs for patients receiving supportive care only

Medication class	Medication assumed (dosage)	Tariff (pack size)	Daily cohort cost (n)	
			GL (66)	PL (31)
Antidiabetic medication				
Insulin (intermediate or long acting, plus fast acting in a 70:30 ratio)	Novorapid Flexpen 100u/ml; Novomix30 Flexpen 100u/ml; Humulin I Kwikpen 100u/ml; Lantus Solostar pen 100u/ml (GL: 625 units; PL: 278 units)	£30.60; £29.89; £21.70 £37.77; respectively (5 x 3 ml pens)	£486.84 (39)	£94.39 (17)
Biguanides	Metformin (500 mg/day)	£1.18 (28 x 500 mg tablets)	£1.31 (31)	£0.72 (17)
Thiazolidinediones	Pioglitazone (30 mg/day)	£1.68 (28 x 30 mg tablets)	£0.12 (2)	£0.72 (12)
Sulfonylureas	Gliclazide (80 mg/day)	£0.99 (28 x 80 mg tablets)	£0.00 (0)	£0.18 (5)
Lipid lowering therapies				
HMG CoA Reductase inhibitors	Atorvastatin (20 mg/day)	£0.99 (28 x 20 mg tablets)	£0.39 (11)	£0.42 (12)
Other lipid modifying agents	Colesevelam (2500 mg/day)	£115.32 (180 x 625 mg tablets)	£25.63 (10)	£38.44 (15)
Fibrates	Bezalip Mono (400 mg/day)	£7.63 (30 x 400 mg tablets)	£6.36 (25)	£4.32 (17)
Other concomitant medications (antihypertensives)				
Lisinopril	Lisinopril (20 mg/day)	£0.98 (28 x 20 mg tablets)	£0.32 (9)	£0.25 (7)

Enalapril	Enalapril (20 mg/day)	£2.14 (28 x 20 mg tablets)	£0.54 (7)	£0.23 (3)
Total and average costs				
Total daily cohort costs			£521.49	£139.67
Average daily cost per patient			£7.90	£4.51
Average annual cost per patient			£2,886.00	£1,645.61
Based on Tables 121, 122, 123, 124, 125, 126 and 127 from Appendix 13 in the CS.[1] 1Defined as the subgroup of patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L. All calculations for PL group are based on PL subgroup baseline medications. GL = generalized lipodystrophy; HMG CoA = 3-Hydroxy-3-methylglutaryl-coenzyme A; mg = milligram; PL = partial lipodystrophy.				

The same medications that are provided as supportive care to patients receiving only this treatment are also assumed to be provided for patients receiving metreleptin. However, based on input from the Delphi Panel it is assumed that these medications can be discontinued or their dose reduced for some patients receiving metreleptin. The proportions of patients who, according to the Delphi Panel, could be assumed to either completely discontinue or reduce the dose of specific medications, alongside the anticipated dose reduction for patients who are assumed to reduce their dose, are shown in Tables 5.15 and 5.16.

Table 5.15: Assumed reductions in supportive care medication for patients with PL receiving metreleptin

	Patients able to completely discontinue	Patients able to reduce dose	Anticipated dose reduction for patients able to reduce dose
Insulin	5%	50%	50%
Oral antidiabetic medication	50% (excluding metformin)	35%	50%
Triglyceride-lowering medication (fibrates)	51%	23%	54%
Antihypertensive medication	14%	10%	31%
Source: Table 47 in the CS.[1] PL = partial lipodystrophy.			

Table 5.16: Assumed reductions in supportive care medication for patients with GL receiving metreleptin

	Patients able to completely discontinue	Patients able to reduce dose	Anticipated dose reduction for patients able to reduce dose
Insulin	40%	60%	68%
Oral antidiabetic medication	52% (excluding metformin)	48%	62%
Triglyceride-lowering medication (fibrates)	61%	39%	71%
Antihypertensive medication	17%	12%	32%
Source: Table 48 in the CS.[1]			

GL = generalised lipodystrophy.

In sum, the annual costs that follow from the abovementioned assumptions regarding supportive care medication are shown in Table 5.17 for each treatment arm and for both the GL and PL subgroups of patients.

Table 5.17: Unit costs for each component and total costs of a routine monitoring visit

Drug	Annual costs	Source
Supportive care alone medication cost for GL patients	£2,886.00	NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff[52, 116-118]
Supportive care alone medication cost for PL patients	£1,645.61	NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff [52, 116-118]
Supportive care medication cost for patients with GL taking metreleptin	£674.17	Delphi Panel, NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff[52, 67, 116-118]
Supportive care medication cost for patients with PL taking metreleptin	£1,270.09	Delphi Panel, NIH studies 991265/20010769, NHS prescription cost data, BNF and NHS drug tariff [52, 67, 116-118]
Source: Table 45 in the CS.[1] BNF = British National Formulary; GL = generalised lipodystrophy; NHS = National Health Service; NIH = National Institutes of Health; PL = partial lipodystrophy.		

Other than the costs for medication and routine monitoring, the cost effectiveness model includes the costs that correspond to the health states in the various sub-models for specific forms of lipodystrophy-related complications. These are explained for each sub-model below. In general, the health state costs in the various sub-models are based on previous NICE guidelines or technology appraisal, with complementary inputs sourced from NHS reference costs 2017/2018.[115] Costs were updated to 2018/2019 values using the Hospital and Community Health Services (HCHS) Index (up to 2014 / 2015) and the NHS Cost Inflation Index (NHSCII) (from 2015/2016 and onwards) as provided by the Personal Social Services Research Unit (PSSRU) 2019.[114]

Pancreas sub-model

In absence of any values from previous appraisals or guidelines for the cost of an acute pancreatitis event, this was based on the NHS reference costs 2017/2018 for a finished consultant episode (FCE) for endocrine disorders (using weighted average of elective inpatients KA08A, non-elective long stays KA08B, and non-elective short stays KA08C).[115]

Liver disease sub-model

Assumptions regarding the health state costs in the liver disease sub-model were based on those as reported in the NICE non-alcoholic fatty liver disease (NAFLD) guideline.[66] The health state costs for decompensated cirrhosis with varices and compensated cirrhosis with varices were assumed to be the same as those from the decompensated cirrhosis and compensated cirrhosis health states in the NICE NAFLD guideline.[66] Similar to the assumptions in the NICE NAFLD guideline,[66] liver transplant costs

were assumed to be the same as those in Hepatitis B or C. For the asymptomatic liver disease and advanced fibrosis health states, the costs of were assumed to be the same as non-alcoholic fatty liver - non-alcoholic steatohepatitis (NAFL-NASH) (F012) and Fibrosis F3 in the NICE NAFLD guideline,[66] respectively.

Cardiovascular disease sub-model

The assumptions for the health state costs in the sub-model for cardiovascular disease were based on those made for NICE CG181.[119] The six-monthly costs from NICE CG181 were adjusted to annual costs by adding half the costs of the post-event state to the event state costs. The cost of the angina health state was sourced from NICE NG17.[105]

Kidney disease sub-model

The assumptions regarding the health state costs in the kidney disease sub-model are based on NICE TA597,[109] NICE CG182,[120] and NICE NG17.[105] The assumptions for the costs of the microalbuminuria and macroalbuminuria health states were based on those in NICE TA597.[109] NICE CG182 informed the assumptions regarding the cost of the end-stage renal disease (ESRD) health state that were based on CKD stage 5.[120] The costs for the renal transplant and post-renal transplant health states were sourced from NICE NG17.[105]

Neuropathy and retinopathy sub-model

The same health state costs for the neuropathy and retinopathy sub-model were assumed as in NICE TA597,[109] with the exception of the cost of the amputation health state. Instead of using separate health states for minor and major amputations as in NICE TA597,[109] the company included only a single amputation health state for the current appraisal. The cost of this health state was based on a weighted average, using the prevalence of minor and major amputations as reported on page 31 of the committee papers of NICE TA597,[109] and which is based on data from the National Diabetes Audit 2016-2017[121], in combination with the NHS reference costs for minor (HRG codes YQ24A-YQ26C) and major (HRG codes YQ21A-YQ22B) amputation,[115] under the assumption that all amputations resulting from neuropathy are elective.

An overview of the health state costs in each of the sub-models is provided in Table 5.18.

Table 5.18: Overview of health states costs and their sources for the various sub-models

Sub-model / health state	Base-case value, annual cost (2018/2019)*	Source
Liver sub-model		
Asymptomatic liver disease	£143.39	NAFL-NASH F012 cost from NICE NAFLD guideline[66]
Advanced fibrosis	£462.28	Fibrosis F3 cost from NICE NAFLD guideline[66]
Compensated cirrhosis	£462.28	NICE NAFLD guideline[66]
Decompensated cirrhosis	£13,901.68	NICE NAFLD guideline[66]
Compensated cirrhosis with varices	£462.28	NICE NAFLD guideline[66]
Decompensated cirrhosis with varices	£13,901.68	NICE NAFLD guideline[66]

Variceal bleeding (event cost)	£2,839.18	NICE NAFLD guideline[66]
Hepatocellular carcinoma	£13,901.68	NICE NAFLD guideline[66]
Liver transplant (year 1)	£63,295.43	NICE NAFLD guideline[66]
Post liver transplant (year 2)	£19,659.40	NICE NAFLD guideline[66]
Post liver transplant (year 3+)	£8,984.63	NICE NAFLD guideline[66]
Cardiovascular disease sub-model		
Angina (year 1)	£6,854.89	NICE NG17[105]
Angina (year 2+)	£308.55	NICE NG17[105]
Stroke (year 1)	£4,461.79	NICE CG181[119]
Stroke (year 2+)	£165.87	NICE CG181[119]
Congestive heart failure (year 1)	£3,847.55	NICE CG181[119]
Congestive heart failure (year 2+)	£2,779.05	NICE CG181[119]
Myocardial infarction (year 1)	£3,992.55	NICE CG181[119]
Myocardial infarction (year 2+)	£843.24	NICE CG181[119]
Kidney sub-model		
Microalbuminuria	£39.35	NICE TA597[109]
Macroalbuminuria	£4,026.03	NICE TA597[109]
End stage renal disease	£5,632.97	NICE CG182[119]
Kidney transplant (year 1)	£22,043.99	NICE NG17[105]
Post kidney transplant (year 2+)	£8,233.09	NICE NG17[105]
Pancreatitis sub-model costs (per-event)		
Acute pancreatitis	£1,174.11	NHS reference costs 2017 / 2018: finished consultant episode (FCE) for endocrine disorders; weighted average of elective inpatients KA08A, non-elective long stays KA08B, and non-elective short stays KA08C)[115]
Retinopathy sub-model		
Background retinopathy	£308.42	NICE TA597[109]
Proliferative retinopathy	£1,050.49	
Macular oedema	£3,059.64	
Blindness (year 1)	£5,974.42	
Blindness (year 2+)	£5,772.24	
Neuropathy sub-model		
Peripheral neuropathy	£386.81	NICE TA597[109]
Amputation (year 1)	£6,090.60	Weighted average of minor and major amputations (3:1 ratio),[109] applied to NHS reference costs 2018 – 2019 for minor (HRG codes YQ24A-YQ26C; elective inpatient) and major (HRG codes YQ21A-YQ22B; elective inpatient) amputations[115]
Amputation (year 2+)	£0	NICE TA597[109]

*When needed, costs were updated to 2018 / 2019 values using the HCHS Index (up to 2014/2015) and NHSCII (2015/2016 and onwards) from PSSRU 2019.
Based on Table D8 in the CS.[1]
HCHS = Hospital and Community Health Services; HRG = Healthcare Research Group; NAFLD = non-alcoholic fatty liver disease; NAFL-NASH = non-alcoholic fatty liver -non-alcoholic steatohepatitis; NHS = National Health Service; NHSCII = NHS Cost Inflation Index; NICE = national institute for health and care excellence; PSSRU = Personal Social Services Research Unit.

ERG comment: The ERG considers the implementation of the acquisition costs for metreleptin (based on the doses that patients received in the EAP at Addenbrooke's Hospital including the titration phase), the additional costs due to routine monitoring in the first year of treatment for patients receiving metreleptin (based on the Delphi Panel), and the rates of discontinuation and reductions in use of supportive care medication for patients receiving metreleptin (based on the Delphi Panel) as appropriate.

Since the health state costs in the various sub-models for lipodystrophy-related complications were sourced from guidance documents and clinical guidelines developed by NICE, the ERG considers these costs, as well as their implementation, as appropriate. The costs of micro- and macro-albuminuria in the kidney disease sub-model, the costs of peripheral neuropathy in the neuropathy sub-model, and all health state costs in the retinopathy sub-model were sourced from a previous technology appraisal, with a costing methodology that was approved by the ERG at the time. Therefore, as well as the fact that most of the health state costs used from TA597 were in turn sourced from NG17, the ERG considers these health state costs as appropriate.

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 SoC. The CS also included the results of the deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA).

In the deterministic one-way sensitivity analysis (OWSA) all applicable parameters were varied using either the upper and lower bounds of 95% confidence intervals, or 20% variation if confidence intervals were unavailable.

In the probabilistic sensitivity analysis (PSA), distributions were selected to incorporate the uncertainty around parameter estimates into the model. Where SEs were not available, a SE of 10% of the mean was assumed. The PSA was conducted using Monte Carlo simulations to model 100 cohorts of 200 patients (across two treatments and four patient subgroups) encompassing a total of 160,000 patient runs to ensure stable results. A cost effectiveness acceptability curve (CEAC) was generated through 4,800 patient runs across 43 willingness to pay (WTP) thresholds, totalling 206,400 patient runs to ensure stability.

A number of scenario analyses were also run to assess the impact of varying inputs in a number of plausible scenarios.

ERG comment: The company, in its response to the clarification letter, submitted an updated electronic model. The results of this updated model are presented in Chapter 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.[37]

5.4.1 Deterministic results of the company

The results are presented in Table 5.19 using the approved patient access scheme (PAS). Metreleptin accrued [redacted] incremental QALYs and at an additional cost of [redacted]. This corresponds to an incremental cost effectiveness ratio (ICER) of £179,016 per QALY gained. The ICER has been adjusted according to the NICE HST process guide to reflect the significant QALY gains (>10 incremental undiscounted QALYs) for treated patients, corresponding to an ICER of £155,606. Separate results are also presented for the GL and PL cohorts. These results were based off 10 cohorts of 1,000 simulated patients.

Table 5.19: Company base-case results

Subgroup	Incremental costs (£)	Incremental QALYs	ICER (£)
GL	[redacted]	[redacted]	£128,767 (adjusted)
PL	[redacted]	[redacted]	£176,253 (unadjusted)
Overall (weighted average)	[redacted]	[redacted]	£179,016 (unadjusted) £155,606 (adjusted)
GL = generalised lipodystrophy; ICER = incremental cost-effectiveness ratio; PL = partial lipodystrophy; QALYs = quality adjusted life years			

5.4.2 Sensitivity analyses presented within the company's submission

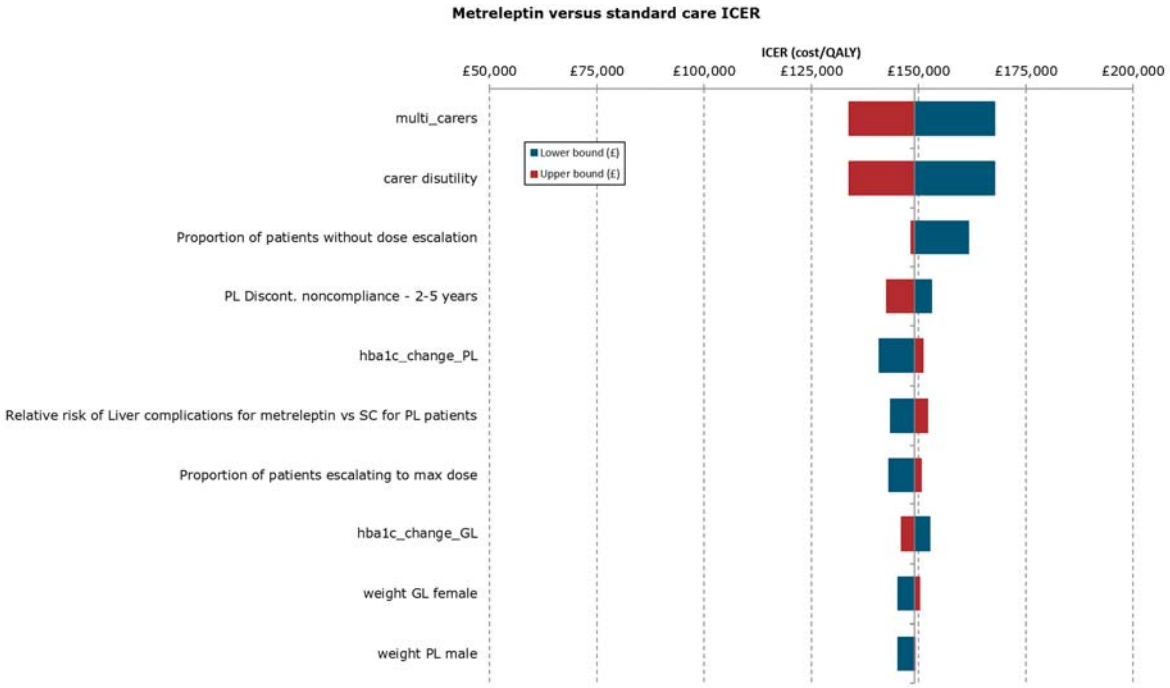
The company conducted a number of sensitivity and scenario analyses. The results of all these analyses are summarised below. Only discounted results are presented here.

5.4.2.1 Sensitivity analyses

Sensitivity analyses included deterministic (DSA) and probabilistic sensitivity analyses (PSA).

The results of the deterministic one-way sensitivity analysis (OWSA) are presented in Figure 5.10. One-way analyses were conducted by analysing 1 cohort of 200 patients for the base-case scenario, and for each of the upper and lower bounds of each parameter. A fixed "seed" of 200 cycles worth of random values was used to ensure comparability of results – ensuring the only variation in values between each 200-patient cohort was the individual corresponding adjusted value.

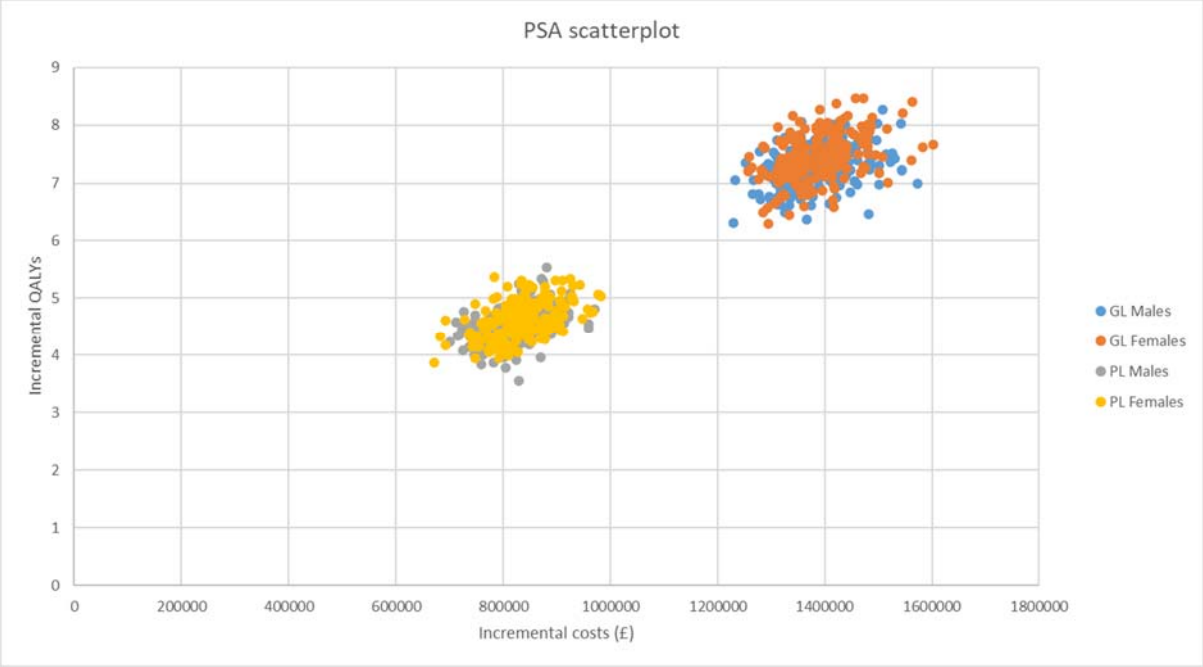
Figure 5.10 One-way sensitivity analysis - ICER results



Source: Figure 1 in the updated cost effectiveness results in the second response to the clarification letter.[37]

PSA was conducted using Monte Carlo simulations to model 200 cohorts of 250 patients encompassing a total of 400,000 patient runs. Results are shown in Figure 5.11.

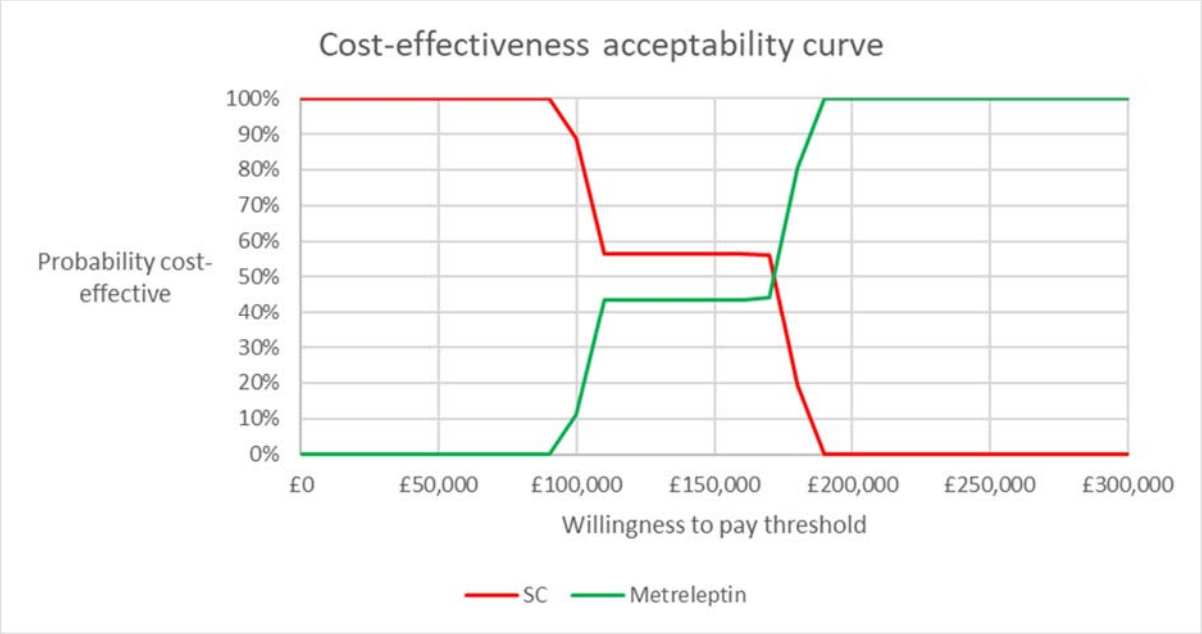
Figure 5.11 Probabilistic sensitivity analysis scatterplot company base case



Source: Figure 2 in the updated cost effectiveness results in the second response to the clarification letter.[37]

A cost effectiveness acceptability curve was run using three cohorts of 1,000 patients per subgroup per threshold (600,000 total patients). Results are shown in Figure 5.12.

Figure 5.12 Cost effectiveness acceptability curve



Source: Figure 3 in the updated cost effectiveness results in the second response to the clarification letter.[37]

5.4.2.2 Scenario analyses

The results of the scenarios run by the company are shown in Table 5.20

Table 5.20: Scenario analyses results

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£) incr. (QALYs)
Base case		£[redacted]	[redacted]	£155,606
Base case with lower discount rates	Metreleptin delivers long-term health benefits to patients. A discount rate of 1.5% for costs and benefits may be considered relevant where long-term health benefits are likely to be achieved.	£[redacted]	[redacted]	£148,822
Liver benefit for metreleptin-treated patients modelled via ALT and AST surrogate outcomes	Relative clinical impact of metreleptin on ALT and AST evaluated in ITC; provides alternative source of benefit on liver outcomes for metreleptin-treated patients.	£[redacted]	[redacted]	£163,645

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£) incr. (QALYs)
Alternative HbA1c reduction for GL and PL = 1.52%	Directly employing the HbA1c reduction estimated in the indirect treatment comparison. NB. UK clinical expert opinion indicate this is an underestimate for patients with GL as it is a pooled analysis.	£[redacted]	[redacted]	£166,976
Additive disutility calculations per cycle	To provide insight to the change in ICER by using standard utility decrement calculations as opposed to conservative multiplicative utility calculations.	£[redacted]	[redacted]	£151,484
Largest single utility decrement per cycle	To provide insight to the change in ICER by using a more conservative assumption than the present multiplicative utility calculations. Single largest utility decrement can be viewed as the minimum utility decrement to patient utility that is likely to happen.	£[redacted]	[redacted]	£164,954
Additive mortality risk inflation	To provide insight into changes in the ICER by using the less conservative assumption of additive mortality risks from different states in the model.	£[redacted]	[redacted]	£157,700
Pancreatitis benefit, OR = 0.93	To provide insight into changes in the ICER by using alternate methodology in the ITC where missing data was imputed.	£[redacted]	[redacted]	£154,340
Mean carer = 1.67	In response to question B12 [37]	£[redacted]	[redacted]	£173,839
FED discontinuation rates: 8.93% in the first year; 5.63% in years 2 to 9; and 2.04% for year 10 and over	Alternative discontinuation rate explored in response to question B8. [37]	£[redacted]	[redacted]	£141,194
Male/female cohorts combined		£[redacted]	[redacted]	£156,675
	Metreleptin – GL patients	£[redacted]	[redacted]	£132,682

Scenario	Assumptions	Incr. costs (£)	Incr. QALYs	ICER (£) incr. (QALYs)
25% additional stopping PL patients, creating 32% overall stopping rate in PL patients	Metreleptin – PL patients	£[redacted]	[redacted]	£156,789
	Metreleptin – all patients	£[redacted]	[redacted]	£146,307
Source: Part 2 of the Clarification response.[37]				

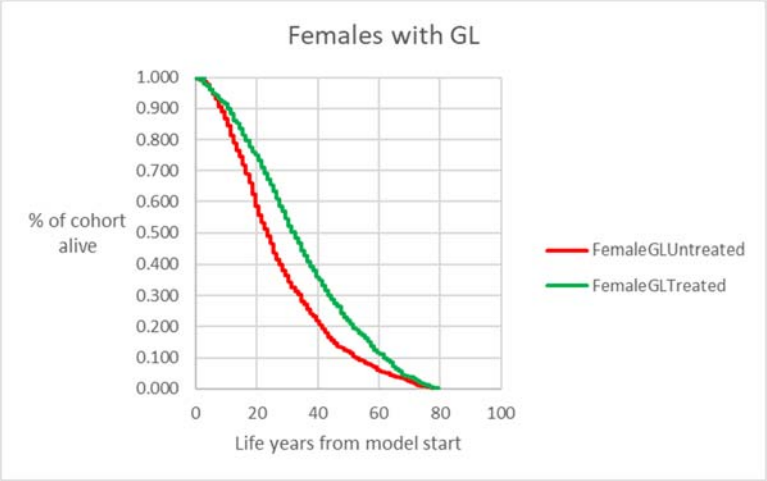
5.4.3 Validation

The company described briefly in section 12.7 of the CS that the model has been quality checked and validated internally and by an external academic modelling expert. In response to question B36, the company stated that an internal health economist independent to those who built the model, conducted a quality check of the model functions and calculations.[37] This included verifying data inputs against their sources, checking the cost year for data inputs, checking distributions assigned to parameters for sensitivity analyses, verifying and validating calculations and functionality, and conducting black-box tests. The company also provided a walkthrough technical videoconference on 10 June 2020.

The company conducted extensive face validity checks using alternate settings and extreme values tests (e.g. removing elements from the model by setting to zero and confirming their absence in model results) to confirm expected results and identify errors. Furthermore, analyses using identical seeded random variables were run to produce identical model results on separate runs and confirm no unexpected or unexplainable variation. In addition, the external academic modelling expert from a leading Evidence Review Group reviewed and validated the Excel model approach and reviewed calculations for errors. As such, the outcomes of these processes were to minimise and remove errors from the model approach.

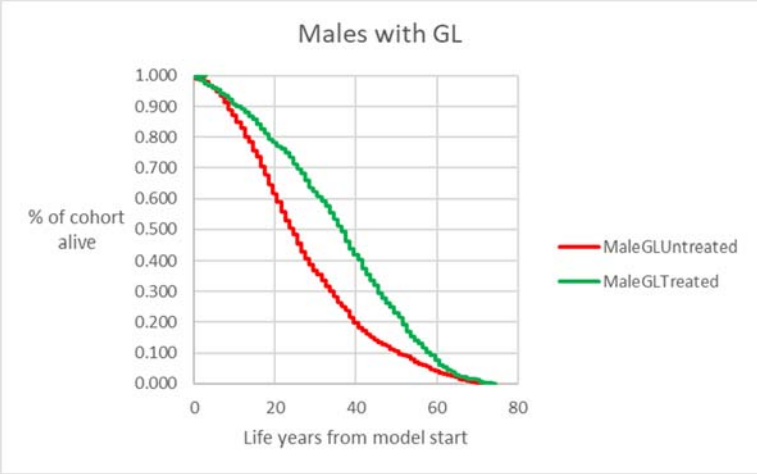
Furthermore, mortality benefits have been validated and compared to existing literature. The life expectancy observed from when patients first enter the model is shown in the figures below. Mean time to death for GL and PL patients has been observed as 51.2 and 66.6 years, respectively, in Akinci et al.[22].

Figure 5.13: Survival of GL, female patients



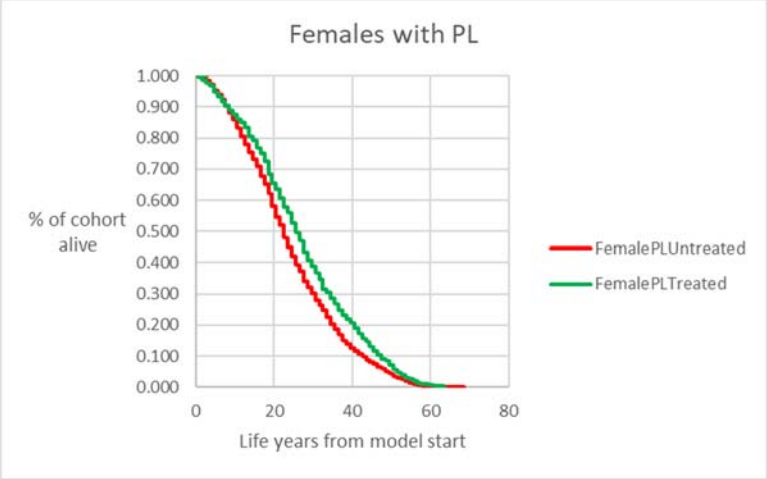
Source: Figure 33 of the CS [1]

Figure 5.14: Survival of GL, male patients



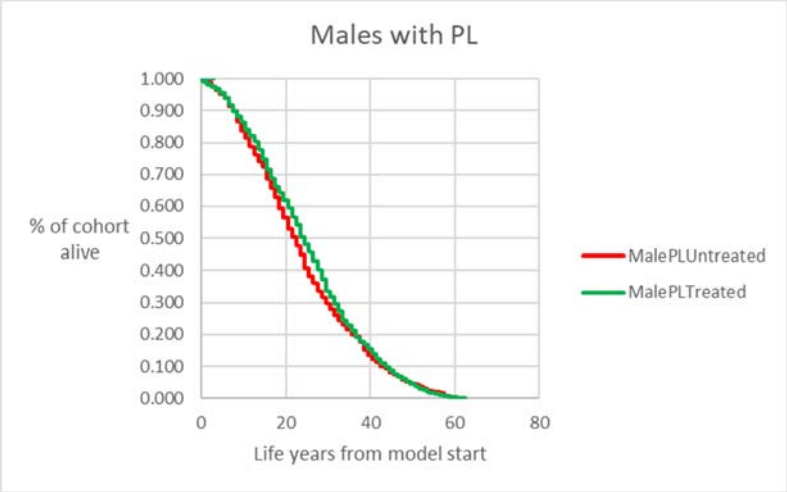
Source: Figure 34 of the CS [1]

Figure 5.15: Survival of PL, female patients



Source: Figure 35 of the CS [1]

Figure 5.16: Survival of PL, male patients



Source: Figure 36 of the CS [1]

ERG comment: It appears that the company has taken the necessary steps to ensure that the model is internally valid, and that the conceptual model was sufficiently validated. These validation steps rely strongly on face validity testing, which is not surprising given the rarity of the disease and lack of any previous model for this disease. The assessment of the operational validity of the model appears to be limited especially with regards to cross-validation testing and validation against empirical data. The cross-validation testing could of course not be done against any other model for treatment of lipodystrophy patients, as no such model was found. However, there was also no attempt to try to validate against other diabetes models to review the outcomes of several sub-models. Regarding the validation against empirical data, this appears to have been done partially by comparing survival in the model against survival reported in the literature, however, it is unclear from the figures 5.13-5.16 how they relate to the mean time to death for GL and PL patients (51.2 and 66.6 years, respectively) as observed in Akinci et al.[22], as this requires an area under the curve calculation that has not been presented with the figures.

5.5 Discussion of the available evidence relating to value for money for the NHS and PSS

The economic model submitted by the company represents an improvement on the previous models related to this appraisal. However, there are some important areas of uncertainty remaining in the economic analysis.

The model structure does reflect suggestions by the NICE committee and is better structured to account for the potential progression of complications related to lipodystrophy over time. However, it remains predicated upon the assumption that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but different aetiology. This is an area of considerable uncertainty.

In the economic model, there is a lack of consistency in the subgroups of lipodystrophy patients used to estimate different parameters, particularly for PL patients. Two different subgroups of PL patients are defined in the NIH studies; PL overall and PL subgroup. The PL subgroup represents a subgroup of the PL overall patients who have at least 6.5% HbA1c level at baseline. Therefore, this PL subgroup represents a more severe group as they are more at risk of organ damage. The company used the PL overall group to estimate the ITC, but the PL subgroup to estimate other model inputs for PL patients from the NIH studies, included baseline characteristics, baseline levels of metabolic surrogates and changes from baseline of HbA1c. It is unclear whether metreleptin will be given to all PL patients in clinical practice, or only those who meet the criteria for the PL subgroup. This treatment decision should be clear and reflected clearly in the model parameters, otherwise it is unclear to what extent model results reflect those PL patients who will receive metreleptin in practice.

Another area of uncertainty in the model is the extent to which lipodystrophy patients will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions. The model structure is certainly an improvement on previous rounds of this appraisal as it is able to use previously validated organ models and surrogate metabolic outcomes to estimate progression of organ damage and final outcomes in lipodystrophy patients. However, the generalisability of the populations used to estimate transition probabilities within each organ sub-model from the literature to lipodystrophy patients cannot be verified.

Similarly, data on utilities are mostly obtained from literature in non-lipodystrophy populations. The few utilities which are specific to lipodystrophy patients are obtained from a single DCE study from the original submission which is associated with substantial limitations and therefore utility estimates used in the model are also subject to uncertainty.

A key area of uncertainty in the model is the long-term efficacy of metreleptin, both while it is still being taken and post-discontinuation. As outlined in the clinical effectiveness section, there is little evidence of the long-term effectiveness of metreleptin in patients continuing treatment. However, a key driver of cost-effectiveness results is the assumption made regarding the post-discontinuation efficacy of metreleptin. The company assumed long-term continued efficacy in terms of HbA1c levels, risk reduction in liver complications and partial lifetime QoL benefits for patients and carers after metreleptin discontinuation. However, no data was provided in the submission on these outcomes post-discontinuation and therefore this remains and important area of uncertainty.

6. IMPACT ON THE COST-CONSEQUENCE ANALYSIS OF ADDITIONAL EXPLORATORY CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Introduction

This Chapter outlines the changes made by the ERG to the cost effectiveness model provided by the company alongside part two of their clarification response.[37] These changes were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[122]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model to form an ERG base-case, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

6.2 Explanation of the ERG adjustments

Six issues previously discussed in section 5 can be seen as errors that were fixed.

1. The ERG identified several errors on the simulation sheet regarding gender distribution calculations and the calculation of the ICER. Both were corrected, (ICER should be the mean incremental cost over all runs divided by the mean incremental QALYs over all runs, not the mean of each ICER calculated from each run) , but the ICER calculation could only be corrected for the unadjusted ICER. The adjusted ICER could not be corrected.

2. The company scenario for the average number of carers assumed a value of two instead of the average of 1.67 from the Lipodystrophy Caregiver Burden Survey.[29] This was corrected.

3. A disutility for the burden of caring of 0.0986 was used in the company model, based on the difference between the average EQ-5D value of 0.8124 from the Lipodystrophy Caregiver Burden Survey and the UK EQ-5D general population norm at the average age of carers in the survey (43.7) of 0.911.[29, 103, 104] However, a different set of EQ-5D general population norms, representative of the UK-England, obtained from the same source were used elsewhere in the model as age-adjusted baseline utilities from which all utility decrements were subtracted. For consistency the ERG prefers to calculate the decrement due to caring based on the same set of general population norms. The UK-England general population norm is 0.893, at the age of 43.7, which results in a disutility due to caring of 0.0806.

4. In the kidney sub- model, the company had calculated RRs, assuming from ORs, however the values assumed to be ORs were in fact HRs. The calculation of RRs was corrected to account for this.

5. The number of pancreatitis events from baseline was entered into the model as 45 but the data provided says there were 30 events. This was corrected.

Additionally, the following issues were discussed in section 5 and can be regarded as matters of judgement.

6. The company adjusted transition probabilities in the liver model for treated patients using an RR estimate from the Delphi panel instead of the ALT/AST data available. The ERG prefers to use available data rather than expert opinion in this case.

7. The way that HbA1c was modelled meant that patients receiving metreleptin received the full treatment benefit in terms of a drop in HbAc1 upon treatment initiation. Thereafter, all patients in the model (whether on treatment with metreleptin, discontinued from metreleptin or receiving SoC) received an annual increase in HbA1c of 0.15%. Therefore, discontinuation had no impact on efficacy in the four organ sub-models using HbA1c to determine transition probabilities. No evidence was provided of the efficacy of metreleptin post-discontinuation. This assumption was therefore considered unrealistic. As per TA315, the ERG modelled a reversal of the treatment effect on HbAc1 in the cycle after discontinuation to remove this assumption of long term continued treatment effect post metreleptin discontinuation.[88]

8. The company also assumed long-term treatment benefit post-discontinuation in the liver model. The ERG removed this assumption as no evidence was provided of post-discontinuation efficacy in terms of the liver.

9. The company model also assumed that 50% of the QoL treatment differential between metreleptin and SoC (assumed to cover issues such as hyperphagia, ability to perform work/schoolwork, physical appearance and PCOS) were maintained after discontinuation from metreleptin for patients and carers over the patient's remaining lifetime. No evidence was represented demonstrating a continued treatment effect in terms of hyperphagia, ability to perform work/schoolwork, physical appearance and PCOS after discontinuation and therefore this assumption was removed by the ERG.

10. In their base-case the company assumed discontinuation rates from the NIH trials based on non-compliance only of 1.5% and 3.86% in GL and PL patients respectively. These rates remained constant over time in the model. However actual discontinuation was higher in the trials. In Part 2 of the clarification response, the company provided final evaluation decision (FED) discontinuation rates of 8.93% in year 1, 5.63% in years 2-9 and 2.04% in years 10 onwards. This closer reflects the discontinuation observed in the first year of the NIH trial and the decline in discontinuation over time seems plausible. Therefore, the ERG used these rates in their base-case.

11. Given the higher rates of discontinuation adopted in the ERG base-case, the company's option to manually assume that an additional 10% of PL patients stop treatment (which was implemented by the company in order to align model discontinuation rates for PL patients with those expected by clinical experts) was turned off.

6.3 ERG base-case results

The results from the ERG deterministic base-case are displayed in Table 6.1 below. This analysis was run using seeded random numbers and a single cohort of 3,000 patients per subgroup (GL/PL,

female/male, metreleptin/SoC) and therefore 8 separate subgroups of 3,000 were simulated. Overall, across both types of lipodystrophy, metreleptin cost an additional [redacted] for a QALY gain of [redacted], resulting in an ICER of £241,531 per QALY gained compared to SoC. Incremental costs were higher in GL patients than PL patients, but this was outweighed by higher incremental QALYs in GL patients, resulting in a low ICER of £201,261 compared to £289,424 in GL and PL patients respectively. As the undiscounted QALY gain was always below 10, no adjusted ICERs were calculated.

Table 6.1 ERG base-case results, discounted

Subgroup	Incr. costs (£)	Incr. LYGs (not discounted)	Incr. QALYs	ICER versus SoC (£/QALY)
GL	[redacted]	[redacted]	[redacted]	£201,261
PL	[redacted]	[redacted]	[redacted]	£289,424
Overall	[redacted]	[redacted]	[redacted]	£241,531

GL = generalised lipodystrophy; ICER = incremental cost-effectiveness ratio; incr. = incremental; PL = partial lipodystrophy; QALYs = quality adjusted life years; SoC = standard of care

Table 6.2 below shows the individual steps implemented to go from the company base-case to the ERG base-case and their cumulative impact on the ICER, as each step is added to the previous changes already implemented. The ERG base-case results were taken from Table 6.1 and the company base-case results from Table 5.20. The intermediate steps were estimated by running a single cohort of 1,000 patients for each of the eight subgroups run in the model using seeded random values. ICERs in bold are adjusted ICERs where some simulations resulted in more than 10 incremental undiscounted QALY gains.

The changes which had the largest impact on the ICER were removing the assumed 50% lifetime continuation of treatment benefits on patient and carer QoL post-discontinuation from metreleptin, amending the disutility due to caring and the average number of carers per patient and removing the post-discontinuation benefit in the liver model.

Table 6.2 Cumulative impact of the ERGs preferred model assumptions

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	Cumulative Unadjusted ICER (£/QALY)	Cumulative Adjusted ICER (£/QALY)
Company base-case		[redacted]	[redacted]	Not provided	**£151,868***
Company updated base-case (after clarification)	5.4	[redacted]	[redacted]		**£155,606*§**
ERG change 1 – Corrected gender weighting in result and non-adjusted ICER calculation	6.2	[redacted]	[redacted]	£183,442	**£156,859***
ERG change 2 – Average number of carers corrected to 1.67 (not in company BC)	5.3.3.7	[redacted]	[redacted]	£183,442	**£156,859***

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	Cumulative Unadjusted ICER (£/QALY)	Cumulative Adjusted ICER (£/QALY)
ERG change 3 – RR calculated from HRs instead of assumed ORs	5.3.3.1	[redacted]	[redacted]	£183,456	**£156,795***
ERG change 4 – Corrected number of pancreatitis events from baseline from 45 to 30	5.3.3.1	[redacted]	[redacted]	£182,275	**£153,682***
ERG change 5 – Disutility for burden of caring amended to 0.0806 from 0.0986	5.3.3.7	[redacted]	[redacted]	£197,516	**£170,609***
ERG change 6 – Use average number of carers (1.67) instead of multi carer assumption (2)	5.3.3.7	[redacted]	[redacted]	£210,544	**£185,448***
ERG change 7 – Adjust transition probabilities in treated patients in liver model using ALT/AST data instead of Delphi assumption	5.3.3.1	[redacted]	[redacted]	£214,826	**£193,970***
ERG change 8 – Post-discontinuation treatment benefit in HbA1c removed	5.3.3.1	[redacted]	[redacted]	£219,718	**£200,038***
ERG change 9 – Post-discontinuation treatment benefit in liver model removed	5.3.3.1	[redacted]	[redacted]	£227,186	**£211,296***
ERG change 10 – 50% post-discontinuation treatment benefit in QoL removed and 50% post-discontinuation carer benefit in QoL removed	5.3.3.7	[redacted]	[redacted]	£263,698	**£265,015***
ERG change 11 – FED discontinuation rates used instead of only accounting for discontinuation for non-compliance	5.3.3.6	[redacted]	[redacted]	£240,478	£252,379
ERG change 12 – Additional 10% PL patients stopping treatment removed	6.2	[redacted]	[redacted]	£241,531	£251,091

Preferred assumption	Section in ERG report	Inc. Costs (£)	Inc. QALYs	Cumulative Unadjusted ICER (£/QALY)	Cumulative Adjusted ICER (£/QALY)
*ICERs in bold are adjusted as some simulations provide more than 10 undiscounted QALYs. Non-bolded adjusted and unadjusted ICERs differ only due to the ERG correction of the ICER calculation, not because any runs provide more than 10 undiscounted QALYs §This ICER was not run with a fixed seed, so the difference between this ICER and the first ERG adjusted ICER is due to random variation. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = base-case; FED= final evaluation decision; HR = hazard ratio; ICER = incremental cost effectiveness ratio; inc. = incremental; ITC = indirect treatment comparison; OR = odds ratio; PL = partial lipodystrophy; QALY = quality adjusted life year; QoL = quality of life; RR = relative risk.					

The ERG also conducted a PSA of their preferred base-case, with results displayed in Table 6.3. For the PSA we ran 400 PSA iterations with 300 patients per iteration. This yielded a probabilistic ICER of £242,987, which aligns quite closely with the deterministic result of £241,531. Note that in all PSA runs the incremental undiscounted QALY gain stayed below 10.

Table 6.3 ERG probabilistic base-case results

Subgroup	Incr. costs (£)	Incr. QALYs	ICER versus SoC (£/QALY)
GL	[redacted]	[redacted]	£202,699
PL	[redacted]	[redacted]	£290,651
Overall	[redacted]	[redacted]	£242,987
GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; incr. = incremental; PL = partial lipodystrophy; QALYs = quality adjusted life years; SoC = standard of care			

Figure 6.1 presents the scatterplot of the PSA outcomes on the CE-plane. Both for the GL and the PL population, the outcomes for male and female patients are more or less the same. When comparing GL versus PL, we see that the latter group clearly has lower QALY gains, for just slightly lower additional costs. Based on these PSA outcomes we also constructed the CEACs, in Figure 6.2. Here we clearly observe that for the GL population the probability of being cost effective only becomes larger than 0 if a threshold ICER of over £150,000 is assumed. For the PL population a threshold ICER of over £200,000 would be needed for the probability of being deemed cost effective to rise above zero.

Figure 6.1 PSA scatterplot ERG base case

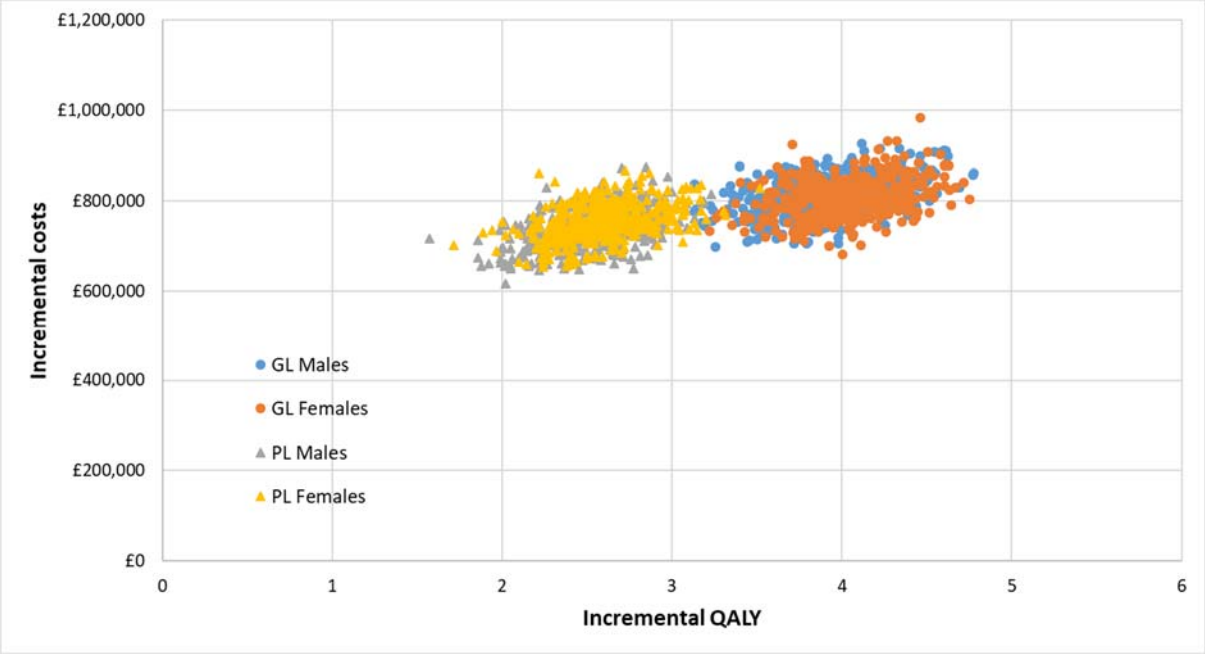
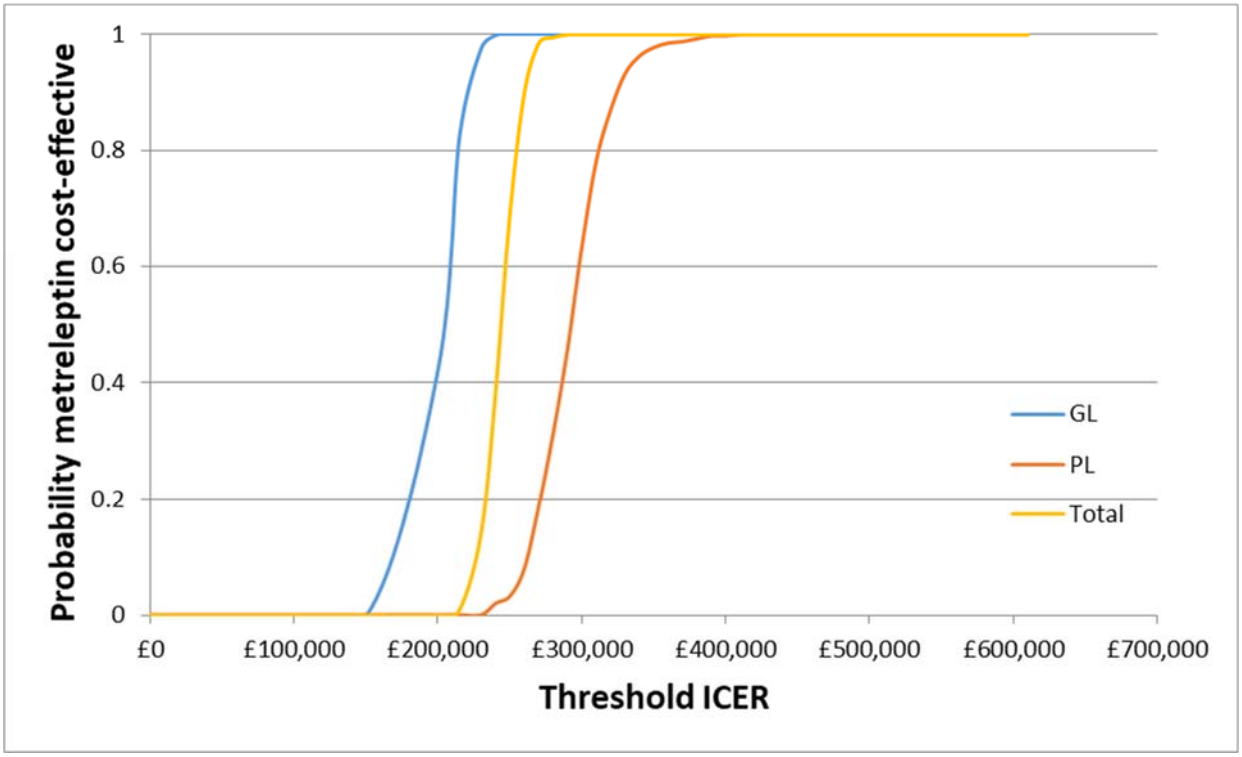


Figure 6.2 Acceptability curve ERG base case



6.4 Exploratory scenario analyses conducted by the ERG

The ERG conducted 10 additional scenario analyses to explore input parameter uncertainty. The scenarios are presented in Table 6.4 and described below:

- Scenario 1: Using the baseline characteristics of the full analysis set (FAS) and overall PL population instead of safety analysis set (SAS) and PL subgroup
- Scenario 2: Using the available baseline characteristics of the Addenbrooke' EAP patients.

- Scenario 3: Turning off the reversal of HbA1c
- Scenario 4: Changing the discontinuation rates to 1.5% for GL and to 3.86% for PL, which are the annual discontinuation rates due to non-compliance from the NIH studies.
- Scenario 5: Changing the discontinuation rates to 7.91% for GL and to 10.76% for PL, which are the annual discontinuation rates due to all reasons from the NIH studies.
- Scenario 6: Assuming post-discontinuation treatment benefits for HbA1c, liver and QoL
- Scenario 7: Assuming a single carer per patient
- Scenario 8: Using 2 carers per patient
- Scenario 9: Using average carer and company's base-case value for carer disutility -0.0986
- Scenario 10: Using pancreatitis disutility -0.06 from the reanalysis of the DCE study

Table 6.4 ERG scenario results

Scenario	Description	Incremental Costs versus SoC (£)	Incremental QALYs versus SoC	ICER (£) versus SoC
Base case		[redacted]	[redacted]	£241,531
Scenario 1	Baseline characteristics from FAS and PL overall	[redacted]	[redacted]	£239,923
Scenario 2	Baseline characteristics from Addenbrooke's EAP	[redacted]	[redacted]	£276,555
Scenario 3	Turn off reversal of HbA1c	[redacted]	[redacted]	£235,930
Scenario 4	Discontinuation rates: GL 1.5%, PL 3.86%	[redacted]	[redacted]	£277,393
Scenario 5	Discontinuation rates: GL 7.91%, PL 10.76%	[redacted]	[redacted]	£264,580
Scenario 6	Assuming post-discontinuation treatment benefits for HbA1c, liver and QoL	[redacted]	[redacted]	£174,492
Scenario 7	Single carer per patient	[redacted]	[redacted]	£278,250
Scenario 8	2 carers per patient	[redacted]	[redacted]	£228,469
Scenario 9	Carer disutility = -0.0986 (company base-case)	[redacted]	[redacted]	£226,750
Scenario 10	Pancreas disutility = -0.06	[redacted]	[redacted]	£242,736

EAP = early access programme; FAS = full analysis set; GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PL = partial lipodystrophy; QALYs = quality adjusted life years; QoL = quality of life; SoC = standard of care

Of the 10 scenarios, 6 showed an increase in the ICER compared to the base-case. The scenario which had the largest impact on results was Scenario 6 (£174,492), which assumed post-discontinuation treatment benefits for HbA1c, liver and 50% post-discontinuation benefit for the QoL of patients and

carers. Scenario 7, where only one care giver per patient was assumed, had the second highest impact on the results with an ICER of £278,250 per QALY gained.

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 mostly lacking.

One study (Chiquette et al. 2017) identified in the literature search was considered by the company but they did not deem it accurate or generalisable for a UK population and the metreleptin licence.[123] The study conducted a search of five electronic medical record databases and literature searches to quantitively estimate the prevalence of lipodystrophy, but according to the company there were issues regarding the search strategy used, a the lack of data presented for lipodystrophy subgroups (GL and PL subgroup), and uncertain assumptions used to obtain prevalence estimates.

Instead, the company used the EAP data to estimate patient numbers for the budget impact analysis. As the EAP has been running for 10 years now, the company contends that the number of patients on the programme is a good indicator of the number of eligible patients in the UK.

Clinicians from Addenbrooke's Hospital in England who are involved in the UK EAP have provided expert opinion to estimate the number of new GL and uncontrolled PL patients, who present each year and would be eligible for metreleptin. Based on expert clinical opinion, it is assumed that [redacted] new patients each year would be eligible for lipodystrophy treatment ([redacted] for GL and [redacted] for PL). From EAP data and expert opinion the expected number of patients eligible over the next five years are presented in Table 7.1.

Table 7.1 Company budget impact analysis

	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 (+)	£1,011	£985	£983	£1,001	£998
Gross medicines costs per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased disease management costs (1st year) (+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost (-)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patient total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	NA	85%	90%	90%	90%
Discontinuation rate GL (non-compliance)	1.5%	1.5%	1.5%	1.5%	1.5%

	Year 1	Year 2	Year 3	Year 4	Year 5
Discontinuation rate PL (non-compliance / stopping rule)	3.86%/ 19.27%	3.86%/ 19.27%	3.86%/ 19.27%	3.86%/ 19.27%	3.86%/ 19.27%
Number of patients treated total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adapted from Tables 54, 55 and 57 in the CS and Table 18 in part 2 of the response to the CL [1, 37] GL= generalised lipodystrophy; PL= partial lipodystrophy					

The company assumes that the uptake rate will rise from 85% in year 1 to 90% in year 5, based on clinical expert opinion. Adherence is assumed to be 100%. Annual discontinuation rate comprised of treatment non-compliance from NIH studies 991265/200110769 (1.50% for patients with GL and 3.86% for patients with PL) and stopping rules (0% for patients with GL and 19.27% for patients with PL), which are consistent with the cost-effectiveness analysis.[48] The resulting number of patients treated per year is presented in table 7.1.

According to the company, the budget impact analysis assumes for the treatment costs 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.

Additionally, the Delphi Panel convened by the company suggested that there would be supportive care savings owing to reductions in usage of insulin, oral antidiabetic medication, lipid lowering therapies and antihypertensive medications. These savings amount to £2,212 per patient with GL and £376 per patient with PL. Furthermore, the Delphi Panel also suggested that treatment with metreleptin increases disease management costs by £651 during the first year of treatment, as two extra visits are required during the first year.

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. Based on the study found by the company,[123] one might expect a GL population over the age of two years of between 15 to 62 patients. For the PL population over 12 years the prevalence would be about 94-160 patients. These are estimates for all PL patients, not just those with uncontrolled disease. Based on these values it appears reasonable to assume that the number of patients eligible and referred for treatment will continue to rise over the next five years.

The high uptake rate assumed by the company also appears plausible, given the current lack of treatment alternatives and the long experience in the UK with metreleptin treatment.

However, some issues arise in the calculation of the company. In the calculation of the company, a cost of £1,002 (year 1) to £1,032 (year 5) is added to the treatment costs, labelled 'Supportive medicines cost per patient per annum'. However, it is unclear to the ERG what these costs entail. The increase in costs for hospital visits during the first year of treatment has only been applied in year 1 of the calculations, this not taking into account those patients starting treatment in year 2 to year 5.

Finally, the company assumes that patients will only stop treatment for non-compliance, which is associated with discontinuation rates of 1.5% and 3.86% for GL and PL, respectively. If we use the wider definition of discontinuation like in section 6, these discontinuation rates would amount to 8.93% in the first year of treatment and 5.63% in subsequent years.

To account for the increase in costs in the first year, and the higher discontinuation rate in the first year, we have repeated the calculations from the company (Table 7.2), but now making a difference between incident patients and prevalent patients. Incident patients are those who start treatment in a year, prevalent patients have had at least 1 year of treatment already.

Table 7.2 ERG budget impact analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition costs per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased disease management costs per incident case (+)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Displaced medicines cost per patient per annum (-)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident GL eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incident PL eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	-	85%	90%	90%	90%
Discontinuation rate incident cases GL	8.9%	8.9%	8.9%	8.9%	8.9%
Discontinuation rate PL incident cases + stopping rule	8.93%/ 19.27%	8.93%/ 19.27%	8.93%/ 19.27%	8.93%/ 19.27%	8.93%/ 19.27%
Number of incident patients treated GL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of incident patients treated PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent GL patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalent PL patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation rate prevalent cases GL	5.6%	5.6%	5.6%	5.6%	5.6%
Discontinuation rate PL prevalent cases + stopping rule	5.63%/ 19.27%	5.63%/ 19.27%	5.63%/ 19.27%	5.63%/ 19.27%	5.63%/ 19.27%
Number of prevalent patients treated GL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of incident patients treated PL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs drug acquisition - displaced medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs consultations incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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]), all in all somewhat lower than the estimated budget impact from the company. However, since the number of incident patients per year is uncertain as well as the uptake, these budget impact estimates should be regarded as tentative.

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 Proportion of costs or benefits which fall outside of the NHS and PSS

The majority of costs and health outcomes are expected to be captured within the economic analyses presented with treatment and management costs borne primarily by the NHS and PSS.[1] However, the work and productivity loss associated with lipodystrophy can be substantial. Most patients are affected from birth due to genetic/familial disease, with symptoms manifesting in childhood, and therefore carers/families are also heavily affected. Lipodystrophy has been shown to considerably impact patients' independence and ability to work and study. 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 associated co-morbidities, can also lead to impaired or complete inability to work or attend school. While estimates on the impact of lipodystrophy on productivity are not available, the costs of reduced productivity at work (due to people with diabetes not working because of death or poor health or working at a lower level of productivity) are estimated at nearly £9 billion.[124]

Of the 114 patients treated with metreleptin at the NIH, 35% had one caregiver not working or only working part time to support them due to their disease.[125] Following metreleptin initiation, only 7% of these patients had a caregiver not working or only working part time, an 80% reduction. The work-loss impact is also very significant on patients, both due to impaired ability to work as adults as well as impaired schooling as children.[1] 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 and among 64 non-adult patients treated with metreleptin, 59.4% had impaired school attendance. Therefore productivity, both for patients and carers is expected to substantially improve with effective therapy.

8.1.2 Societal costs

Metreleptin is expected to reduce costs to local authority and education bodies. The substantial burden of lipodystrophy on young patients means they may require substantial additional support at school. This is currently unquantified.[1] In the UK, the local authority is bound 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.[126] 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.

8.1.3 Costs borne by patients

Costs borne by patients and carers include travel expenses for bi-annual visits to Addenbrooke's Hospital. Addenbrooke's is the only specialist centre in the UK and therefore overnight accommodation may be required for those travelling further. Other additional travel costs may be incurred to local centres post and prior to diagnosis e.g. to general practitioners or secondary care providers.[1]

Metreleptin is administered subcutaneously and can be self-administered, avoiding unnecessary travel expenses to the hospital for treatment and any associated carer costs (including travel or fees for a private carer to escort a patient to the hospital). It also avoids patients and their family members taking unnecessary time off work to attend or escort patients to regular appointments required for treatment.[1]

Other potential costs may include fertility treatment and cosmetic treatment, which are not always reimbursed by the NHS.[1]

8.1.4 Other carer costs

The Lipodystrophy caregiver disease burden survey captured feedback on the burden of disease for caregivers, and associated resource use.[29] Carers indicated that balancing caring responsibilities alongside other responsibilities can impact their ability to work and the possibility of having personal time. In response to the question "Have you had to give up your work/study, reduce your hours, change your type of work/study or retire early due to caring responsibilities?", 43% of respondents answered "Yes". Of those who indicated yes, they reported missing 2 to 12 hours of work per week due to caring responsibilities. Balancing carer responsibilities alongside other responsibilities can also leave carers strained for personal and social time, including time spent with other family members. Inability to work could have financial implications for carers and loss of personal time could lead to increased mental burden which in turn could impact ability to work in the future.

8.1.5 Impact of the technology on research and innovation

During the development of metreleptin, the company has engaged in a comprehensive evidence generation programme to strengthen the evidence base on the understanding of lipodystrophy and the clinical effectiveness of metreleptin.[1] Key recent contributions include:

- Assessing the organ abnormality burden and its progression, and mortality
- Assessing the burden of disease and performance of metreleptin in lipodystrophy patients enrolled in the EAP, including patients treated in England at Addenbrooke's Hospital
- Characterising the broad and profound impact of metreleptin on lipodystrophy patients beyond HbA1c and triglycerides, but also organ abnormalities, mortality, hyperphagia, reproductive dysfunction, work/school impact on patients and their carers

The company is committed to continue to support such evidence generation, and hopes that based on its reimbursement in the UK, it will be able to continue to support the lipodystrophy community via Addenbrooke's Hospital data collection and ECLip in the future including a more comprehensive review of the burden of disease and performance of metreleptin in UK and other EAP patients via the Addenbrooke's Hospital data collection and ECLip.

Metreleptin is the first and only licensed medicine for the treatment of lipodystrophy which targets the underlying cause of the disease (leptin deficiency) and provides a step-change in the management of this severe debilitating disease.[1] As a result, metreleptin has the potential to dramatically improve patients' lives via slowing disease progression, which has not been achievable before. However, ground-breaking advances in healthcare such as metreleptin are only meaningful when they reach the people who need them.[1] Reimbursement of metreleptin would enable the company to continue to invest in the vital innovation and collaboration required to meet unmet patient and health system needs in the future.

Enhanced data collection and patient registries are also included described in the company submission. The EClip registry supports the data collection requirements in relation to the EMA's exceptional

circumstances authorisation of metreleptin.[1] The aim of EClip is to compile data on the natural history of each different sub-group of lipodystrophies in patients not exposed to metreleptin, their comorbidities, treatment options used and medical and quality of life out-come for the patients.

Data will continue to be collected at Addenbrooke's Hospital, to provide real-world evidence of relevant outcomes in clinical practice of lipodystrophy patients receiving metreleptin, in order to review its on-going clinical effectiveness. Furthermore, a stopping criterion for metreleptin in PL patients has been applied as part of this appraisal. Additionally, the Addenbrooke's Hospital EAP is reviewing their current approach to data collection and has set-up an enhanced data collection for patients receiving metreleptin from the anticipated date of NICE issuing a positive recommendation for the use of metreleptin in January 2021.[127] Data collection will be enhanced via the introduction of new outcomes and timeframes to be collected including ALT, AST, platelet count and eGFR.

ERG comment: The ERG agree that the majority of costs and health outcomes have been included in the economic analyses within the appraisal. The ERG also agrees that the improvement of symptoms in patients taking metreleptin will likely reduce costs to other sectors such as education and improve ability to work and productivity. However, data on the likely extent of savings in these sectors relating to improvements in lipodystrophy symptoms are not available.

8.2 Staffing and infrastructure requirements associated with the 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. No additional infrastructure would be required as metreleptin is administered by the patient or carer after treatment initiation.[1]

ERG comment: The ERG agree that staffing and infrastructure requirements for the use of metreleptin are low as, once trained in the technique of subcutaneous injection, patients or carers can administer at home. However, the ERG do note that it seems that patients would always be required to travel to Addenbrookes and therefore there may be future benefit in broadening experience in treating lipodystrophy to other UK centres, which may be associated with costs.

9. DISCUSSION

9.1 Statement of principal findings – clinical effectiveness

Single arm, observational studies of metreleptin treatment found improvements in metabolic outcomes from baseline to month 12 in patients with GL and PL (including the subgroup of patients with PL who had similar metabolic disturbances to those seen in patients with GL i.e. with baseline HbA_{1c} ≥6.5%).

- In study NIH 991265/20010769, mean 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]
- In study FHA101, mean 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]
- 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.[1]
- 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%.[1]

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.[55] 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 hypoglycaemia, autoimmunity, and hypersensitivity.'

The ITC, which was performed using the IPW method in the base case of the CS, showed the following results (See Table 9.1): a statistically significant difference in favour of metreleptin vs. standard care in terms of HbA1c, triglycerides and liver enzymes at 12 months, as well as the odds of pancreatitis. There was, however, a numerical advantage of standard care in terms of all-cause mortality, albeit not significant. These results were confirmed with the use of other methods of adjustment i.e. multivariate regression and IPW+RA.

Table 9.1: Summary of ITC, using IPW method

Outcome	ATE	Robust standard error (%)	95% CI	p-value
Mean change in % HbA1c at 12 months	-1.52	0.38	-2.28 to -0.77	**<0.001***
Mean absolute change in triglycerides at 12 months (mg/dL)	-915.30 [10.34]	225.95 [2.55]	-1358.15 to -472.44 [-15.35 to -5.34]	<0.001*
Mean change in ALT at 12 months (U/L)	-44.13	11.06	-65.81 to -22.46	<0.001*
Mean change in AST at 12 months (U/L)	-27.79	6.93	-41.38 to -14.20	<0.001*

Outcome	ATE	Robust standard error (%)	95% CI	p-value
Odds ratio, pancreatitis	0.94	0.026	0.89 to 0.98	0.01*
Hazard ratio, all-cause mortality	1.38	0.40	0.88 to 20.37 (lower limit corrected by ERG)	0.42

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; w / wo, With or without; RA, regression adjustment.
*denotes significance at the p<0.05 level
[a]**Provided in response to clarification.**[37]

9.2 Statement of principal findings – cost effectiveness

The company presented a de novo cost effectiveness analysis estimating the cost effectiveness of metreleptin compared to SoC in patients with lipodystrophy. The company base-case indicated that metreleptin provided patients with [redacted] incremental QALYs at an incremental cost of [redacted]. This resulted in an ICER of £179,016 per QALY gained. This ICER was adjusted according to the NICE HST process guide to reflect the significant QALY gains (>10 incremental undiscounted QALYs) for treated patients, leading to a final ICER of £155,606.

The ERG corrected several errors and amended some of the company assumptions where they felt these were not supported by data or where other assumptions were deemed more appropriate by the ERG. In the ERG base-case, metreleptin cost an additional [redacted] and provided a QALY gain of [redacted], resulting in an ICER of £241,531 per QALY gained compared to SoC. This ICER did not require adjustment as the threshold for incremental undiscounted QALYs was not met. The ERG changes which had the largest impact on the ICER were removing the assumed 50% lifetime continuation of treatment benefits on patient and carer QoL post-discontinuation from metreleptin, amending the disutility due to caring and the average number of carers per patient and removing the post-discontinuation benefit in the liver model. The PSA yielded a probabilistic ICER of £242,987, which aligns quite closely with the deterministic result of £241,531. Note that in all PSA runs the incremental undiscounted QALY gain stayed below 10. The ERG scenarios which had the largest impact on results were assuming post-discontinuation treatment benefits for HbA1c, liver and 50% post-discontinuation benefit for the QoL of patients and carers (£174,492 per QALY gained) and assuming only one care giver per patient (£278,250 per QALY gained).

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 company has used the best available evidence on both metreleptin and standard care in the form of the NIH follow-up and the GL/PL natural history study respectively to perform an ITC.

- The ITC has been performed using a number of recommended methodologies, in order to test the robustness of the results.
- The economic model is better structured to capture the progressive impact of lipodystrophy on affected organ systems and uses previously validated organ models and metabolic surrogate outcomes to predict final outcomes in lipodystrophy patients, as suggested by the committee in the previous appraisal.
- 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 on clinically important outcomes such as organ damage, such as of the liver, heart and kidneys. The ITC only estimated outcomes for period no longer than 12-months on surrogate outcomes, except for all-cause mortality and pancreatitis.
- The CS lacks information about the effects of metreleptin treatment on the important patient-perceived outcome of hyperphagia.
- The results for the NIH follow-up study and the GL/PL natural history study, which were used to inform the ITC and the cost effectiveness model, were not included in the clinical effectiveness section of the CS.
- The main studies of the CS and those used to inform the ITC lacked 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.
- Participants in the NIH follow-up study and the GL/PL natural history study were not comparable and it is not clear that the ITC reported in the CS was adequate to account for the apparent differences. In particular, it is unclear that sufficient relevant baseline characteristics were included to perform the adjustment.
- 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.[55] 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 hypoglycaemia, autoimmunity, and hypersensitivity.'[55]
- Many of the transition probabilities and utility values used in the organ sub-models are taken from the literature and it is unclear to what extent these input values are generalisable to lipodystrophy patients.
- The company reported that the ITC could not be performed separately for GL and PL patients and therefore the ITC was only used in the pancreas and liver sub-models (although the company chose to use estimates of treatment effectiveness from the Delphi panel rather than the ITC in their base-case in the liver model). All other transition probabilities were taken from the literature and adjusted using HbA1c levels. Baseline and reduction in HbA1c due to metreleptin were estimated from naïve analysis rather than the ITC. Therefore, the ITC had a very minor role in the economic model. This naïve approach limits the reliability of the estimated efficacy of metreleptin in the model.

- The ITC used data from the PL overall group in the NIH studies, whereas patient characteristics used to estimate the outcomes in the economic model were from the PL subgroup, that includes the more severe patients. As he company stated in their response to the clarification letter that they consider the PL subgroup as representative of those patients where standard treatments have failed to achieve adequate metabolic control the model inputs should have consistently reflected this.
- The company assumed long-term continued efficacy of metreleptin post-discontinuation in terms of both HbA1c, risk reduction of liver disease progression and QoL. However, no evidence was presented regarding the post-discontinuation efficacy of metreleptin in any of these areas and therefore these assumptions could not be substantiated.
- The few utility values available from lipodystrophy patients are from a single study which is associated with substantial study design issues, making the resulting utility values very uncertain.
- Several errors had to be corrected in the model including: the average number of carers per patient, the number of pancreatitis events at baseline in the NIH studies, the calculation of some RRs in the kidney sub-model and the calculation of the final ICER in the model.

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 included only very limited evidence about patient perceived symptoms (hyperphagia) and clinical outcomes (liver damage) and data were limited to one year. The 'post-metreleptin improvements' reported in the NIH follow-up study,[45] but not in the CS, were frequently based on measures taken at one year and used 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[45] also included some information on newly emergent (on metreleptin treatment) lipodystrophy characteristics in patients with no evidence of these characteristics prior to metreleptin initiation. 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 included some information on the persistence (up to 36 months) of changes in HbA_{1c} and triglycerides on metreleptin treatment (see Section 4.2.4). However, 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 (88%) developed antibodies to metreleptin.[1] 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.[46] These cases raise concern that development of neutralising antibodies to metreleptin could impair metabolic control and immune function.[55]

The observed effects of metreleptin were 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 natural history study, used to provide comparator data for the ITC had a population which was not comparable to those included in the metreleptin

intervention studies. The company have therefore performed adjustments to control for confounding, but with only three covariates and with varying degrees of success with regards to balancing those covariates. Furthermore, even after adjustment and by several different methods, survival was worse with metreleptin, albeit not statistically significantly.

There is also some uncertainty regarding the applicability of the ITC results to UK clinical practice in that the outcomes that were coprimary, triglyceride and HbA1c changes, were worse for the EAP than the NIH 991265/20010769 study and also the NIH follow-up study results that were used in the ITC and thence in the CEA. Given that the EAP includes only UK patients at Addenbrooke's Hospital, it might be that changes in some outcomes might not be realised in UK clinical practice. On reflection, the ERG would therefore recommend consideration of the performance of the ITC using data from the EAP, particularly for HbA1c and triglycerides.

It is unclear what criteria will be used to determine which patients with PL will receive metreleptin treatment. The EMA marketing authorisation, for PL, is for adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. The CS indicates that the company considers that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is the PL population most considered to best reflect the licensed indication. Leptin levels were part of the PL subgroup definition in NIH studies 991265/20010769, via the inclusion criteria (NIH 2001769: <12.0 ng/mL in females, <8.0 ng/mL in males and <6 ng/mL in children 6 months- 5 years; NIH 991265: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males). The PL subgroup population in the Addenbrooke's EAP (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is therefore similar to that in the NIH studies 991265/20010769. It should be noted, however, that some PL patients who did not meet these baseline metabolic criteria have been treated in the Addenbrooke's EAP.

In the economic model, there is a lack of consistency in the subgroups of lipodystrophy patients used to estimate different parameters, particularly for PL patients. Two different groups of PL patients are defined in the NIH studies; PL overall and PL subgroup. The PL subgroup represents a subgroup of the PL overall patients who have baseline levels of HbA1c ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L. Therefore, this PL subgroup represents a more severe group as they are more at risk of organ damage. The company used the PL overall group to estimate the ITC, but the PL subgroup to estimate other model inputs for PL patients from the NIH studies, included baseline characteristics, baseline levels of metabolic surrogates and changes from baseline of HbA1c. It is unclear in practice whether metreleptin will be given to all PL patients, or only those who meet the criteria for the PL subgroup. This treatment decision should be clear and reflected clearly in the model parameters, otherwise it is unclear to what extent model results reflect those PL patients who will receive metreleptin in practice.

Another area of uncertainty in the model is the extent to which lipodystrophy patients will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions. The model structure is certainly an improvement on previous rounds of this appraisal as it is able to use previously validated organ models and surrogate metabolic outcomes to estimate progression of organ damage and final outcomes in lipodystrophy patients. However, the generalisability of the populations used to estimate transition probabilities within each organ sub-model from the literature to lipodystrophy patients cannot be verified.

Similarly, data on utilities are mostly obtained from literature in non-lipodystrophy populations. The few utilities which are specific to lipodystrophy patients are obtained from a single DCE study from the

original submission which is associated with substantial limitations and therefore utility estimates used the model are also subject to uncertainty.

A key area of uncertainty in the model is the long-term efficacy of metreleptin, both while it is still being taken and post-discontinuation. As outlined in the clinical effectiveness section, there is little evidence of the long-term effectiveness of metreleptin in patients continuing treatment. However, a key driver of cost-effectiveness results is the assumption made regarding the post-discontinuation efficacy of metreleptin. The company assumed long-term continued efficacy in terms of HbA1c levels, risk reduction in liver complications and partial lifetime QoL benefits for patients and carers after metreleptin discontinuation. However, no data was provided in the submission on these outcomes post-discontinuation and therefore this remains and important area of uncertainty.

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Appendix 1

Cochrane Library search syntax errors

The syntax in the reported Cochrane library search strategy appears incorrect. The CS states the advanced search strategy option on the Cochrane Library website was used. The search uses the adj proximity operator, this is not a valid proximity operator in this host and the search terms within the strategy using this are not likely to return any results. The correct proximity operators in this database are NEAR or NEXT. This resource also does not support the use of phrases combined with wildcards. There are numerous phrases in the reported CS strategy combined with wildcards, again this will not have returned expected results if any.

CRD database search syntax errors

The condition term lipodystrop was used in the Company CRD strategy reported in the response to clarification. This resource requires a wildcard symbol at the end to search for truncated terms, so the search term should have looked like this to have retrieved results: lipodystrop*. However, the ERG tested correct strategies and they errors were inconsequential.

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 to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **29 July 2020** 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 ERG Model Implementation Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG's post-discontinuation treatment benefit in HbA1c has been incorrectly implemented in the model. The suggested implementation is as follows: *Table 6.2, page 157:* "ERG change 9 – Post-discontinuation treatment benefit in HbA1c removed" In the process of implementing this change in the economic model, the 0.15% annual drift for untreated patients has been removed, which is not justified and we would assume, unintended.	All results in Tables 1.2, 6.1, 6.2, 6.3 and 6.4 and Figures 6.1 and 6.2 should be updated in light of the implementation error. The following correction is required in the ERG's economic model: Current formula in the model with ERG changes in the 'Model Engine sheet', cell Q82: "=IF(Q72=0,(MIN(Q81+IF(treatType=1,IF(lipType=0,H28,M28),M28),H47)),(MIN(Q81+IF(treatType=1,IF(lipType=0,H28,IF(AND(F81>0.1,F81<0.9),IF(lipType=0,H28+(-H27),M28+(-M27)),M28))),H47)))" Proposed change to cell Q82 in the 'Model engine' sheet: "=IF(Q72=0,(MIN(Q81+IF(treatType=1,IF(lipType=0,H28,M28),M28),H47)),(MIN(Q81+IF(treatType=1,IF(lipType=0,H28,IF(AND(F81>0.1,F81<0.9),IF(lipType=0,H28+(-H27),M28+(M27)),M28)),**I**	An update is required in the economic model to retain the 0.15% annual drift for untreated patients. This change is required so the economic model results reflects the appropriate HbA1c drift for treated and untreated patients. The impact of this correction alone, reduces the ERG's overall base-case ICER (discounted) from £318,745 to £241,531 per QALY for lipodystrophy patients eligible for metreleptin.	The ERG thanks the company for noting this error. The deterministic results and scenario analyses has been updated. However given an issue in the model provided in response to FAC the ERG have been unable to run rerun the PSA in time as a 24 hour run produced very strange results. The ERG have implemented the company changes into the version of the model in which their original ERG PSA was run and can provided updated PSA results within a couple of days of a request by NICE, given that each PSA can take up to 24 hours to run.

	F(lipType=0,H28,M28)),H47)))" The principle of this change also needs to be implemented in cells Q83 to Q181.		

Issue 2 Carers

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG have stated that an incorrect utility value was used for the UK EQ-5D general population norm at the average age of the carers in the survey in various places. For example: *Section 1.11, Page 24 (3rd bullet):* "A disutility for the burden of caring of 0.0986 was used in the company model, based on the difference between the average EQ-5D value of 0.8124 from the Lipodystrophy Caregiver Burden Survey and the UK EQ-5D general population norm at the average age of carers in the survey (43.7) of 0.893. The difference between these values is in fact 0.0806. This was corrected." *Section 5.3.3.7, Page 137:*	The UK EQ-5D general population utility value for the average age of carers in the survey obtained from Janssen *et al* (1) was in fact 0.911 and not 0.893 as stated by the ERG. We believe the ERG was referring to the 'UK-England' utility value when citing a value of 0.893. We propose the following changes to wording to reflect that the UK EQ-5D general population norm at the age of 43.7 is 0.911. (1) Removal of statements on page 24 and page 154. (2) On page 137, to update the text to the following: "The UK EQ-5D general population norm at the age of 43.7 is **0.911**. The difference between these values is **0.0986**, which ~~does not~~ reflects the carer decrement used in the	In the CS (see Section 10.1.9, p158, CS), we have stated that we used the UK-specific utility value to represent the UK EQ-5D general population norm. Based on this, the disutility for caregiver burden of 0.0986 has been correctly calculated using the UK-specific tariff and it is incorrect to refer to this as an 'error' throughout the report. The value of 0.893 reported by the ERG represents the 'UK-England' utility value rather than the UK-specific value. The company's approach is consistent with NICE Decision Support Unit (DSU) recommendations in Technical Support Document (TSD) 8 (2) and previous approaches accepted for carer disutility valuations in NICE appraisals, for example HST9,	The company are correct that the source of the issue here is the use of two different sets of values from Janssen in the company analyses. The ERG can now see that the company used the UK EQ-5D value of 0.911 to estimate the disutility due to caring. However, in the model the company provide and use the UK – England general population values (which estimates a utility of 0.893 in individuals aged 43.7). Therefore, for the sake of consistency with the rest of the model the ERG believe that the disutility due to caring should also be estimated using the UK – England value. The text on pages 24 and 154 has been amended to: "A disutility for the burden of caring of 0.0986 was used in the company model, based on the difference

"The UK EQ-5D general population norm at the age of 43.7 is 0.893. The difference between these values is 0.0806, which does not reflect the carer decrement of 0.0986 used in the company model, which currently overestimates the disutility due to caring. This was corrected in the ERG base-case" *Section 6.2, Page 154:* "A disutility for the burden of caring of 0.0986 was used in the company model, based on the difference between the average EQ-5D value of 0.8124 from the Lipodystrophy Caregiver Burden Survey and the UK EQ-5D general population norm at the average age of carers in the survey (43.7) of 0.893.The difference between these values is in fact 0.0806. This was corrected."	company model. ~~which currently overestimates the disutility due to caring. This was corrected in the ERG base-case~~" (3) Remove "ERG change 6: Disutility for burden of caring corrected to 0.0806 from 0.0986" from table 6.2 and scenario 9 in Table 6.4 of the ERG report.	TA473 and TA527 (3–5). The NICE DSU TSD 8 states: "*It is recommended that the methods used to measure HRQL for the caregiver is the same as that used for the patients. This implies the use of the EQ-5D with the UK population tariff*". There is no such recommendation to use the UK-England tariff.	between the average EQ-5D value of 0.8124 from the Lipodystrophy Caregiver Burden Survey and the UK EQ-5D general population norm at the average age of carers in the survey (43.7) of 0.911. However, a different set of EQ-5D general population norms, representative of the UK-England, obtained from the same source were used elsewhere in the model as age-adjusted baseline utilities from which all utility decrements were subtracted. For consistency the ERG prefers to calculate the decrement due to caring based on the same set of general population norms. The UK-England general population norm is 0.893, at the age of 43.7, which results in a disutility due to caring of 0.0806." On page 137 the text has been amended to: "However, no mean EQ-5D value for carers from the Lipodystrophy Caregiver Burden Survey was provided with the submission. This was requested at clarification and reported to be 0.8124 (SE 0.043). The UK EQ-5D general population norm at the age of 43.7 is 0.911, which corresponds with the company base-case disutility of 0.0986. However, the company use a different set of EQ-5D general

			population norms (the UK-England values) from the same publication by Janssen et al. in the rest of the model. The UK-England values are used by the company as age-adjusted baseline utilities from which all utility decrements are subtracted. In order to maintain consistency with the rest of the model, the ERG prefer to use the UK-England EQ-5D general population norm at the age of 43.7 of 0.893 in the calculation of the disutility due to caring in the ERG base-case. This corresponds to a disutility due to caring of 0.0806 in the ERG base-case." The ERG did not remove the change from Table 6.2 or the scenario from Table 6.4 as they still feel that for consistency the EQ-5D UK–England norms used in the model should have been used to estimate the carer disutility, which should therefore have been based on the norm of 0.893.
In various instances, the ERG report states that the number of carers in the model per patient has been 'corrected' to 1.67. For example: *Section 1.11, Page 24:* "The company scenario for the average number of carers assumed a	In light of the description of problem, we propose that "corrected" is changed to "amended" such that it is clear that the company's base-case of 2 carers per patient was intentional, with rationale for the median provided.	As stated in the company submission and the responses to the ERG clarification questions, our base-case assumption of 2 carers per patient represents the most common scenario in practice based on the median number of carers identified in the *Lipodystrophy Caregiver Disease Burden Survey* (6). Given the small sample size (n=7) due to the ultra-	Not a factual error. The company scenario in the model was called "average number of carers" but the value used did not reflect the mean number of carers in the data. When queried in the clarification stage the company responded that this scenario used "a rounded average carer value of 2, as

value of 2 instead of the average of 1.67 from the Lipodystrophy Caregiver Burden Survey. This was corrected." *Section 5.3.3.7,* Page 137: "However, rounding up the mean overestimates the number of carers. This was corrected in the company model and the ERG base-case uses the average value of 1.67." *Section 6.2, Page 154:* "The company scenario for the average number of carers assumed a value of two instead of the average of 1.67 from the Lipodystrophy Caregiver Burden Survey. This was corrected."		orphan nature of the condition, and the potential impact of outliers having a large impact on the mean, the median value is more likely to be representative of the average number of carers in UK clinical practice. As such, it is not appropriate to refer to the use of 2 carers per patient in the company's analyses as 'incorrect' but to reflect this as the company's usage of a median value.	it is most representative of the most common scenario in practice. The mean number of carers from the caregiver survey was 1.67" No mention of medians were made. Therefore, the assumption by the company that 2 represented the average number of carers in the data was corrected by the ERG.

Issue 3 Post-discontinuation benefits

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Upon reviewing the ERG's amended economic model, it appears as though both the 50% post-discontinuation treatment benefit in QoL and the 50% post-discontinuation carer benefits in QoL have been removed, in arriving at the ICER of £318,745. However, table 6.2 mentions only the removal	Table 6.2 appears to indicate that the increase in the cumulative ICER from ERG change 10 to ERG change 11, is solely the result of the removal of the 50% post-discontinuation treatment benefit in QoL; which is misleading. Based on the ERG model changes, it appears as though the aforementioned	Amendment required for clarity.	Amended as suggested.

of post-discontinuation treatment benefit. *Table 6.2, page 157:* "ERG change 11 – 50% Post-discontinuation treatment benefit in QoL removed"	increase in ICER is also a result of the ERG removing the 50% post-discontinuation carer benefits in QoL. We propose that the text is amended to reflect this: "ERG change 11- 50% post-discontinuation treatment benefit in QoL removed **and 50% post-discontinuation carer benefit in QoL removed**"		
Section 1.11, Page 25: "7. As per TA315, the ERG modelled a reversal of the treatment effect on HbAc1 in the cycle after discontinuation to remove this assumption of long term continued treatment effect post metreleptin discontinuation."	To reflect the clinically harsh nature of the proposed amendment by the ERG, we propose the following amendment: "7. As per TA315, the ERG modelled a reversal of the treatment effect on **HbA1c** in the cycle after discontinuation to remove this assumption of long term continued treatment effect post metreleptin discontinuation. **This, however, is an extreme clinical scenario and does not the reflect slowing of disease progression achieved while patients receive metreleptin treatment.**"	To reflect that the ERG's assumption to withdraw benefits post discontinuation reflect an extreme scenario and are not consistent with the expected residual benefits that have accumulated while patients are on metreleptin, slowing disease progression. The maintenance of glycaemic control is supported by evidence from a clinical study examining HbA1c levels after the withdrawal of metreleptin, which showed HbA1c levels and urine glucose excretion did not change during the follow-up period following metreleptin withdrawal (7).	Not a factual error. The company did not present any evidence of continued benefits of metreleptin on HbA1c post-discontinuation and therefore there is no evidence that the removal of the post-discontinuation effect is an extreme clinical scenario.
Section 1.11, Page 25: "8. The company also assumed long term treatment benefit post-discontinuation in the liver model. The ERG removed this assumption as no evidence was provided of	To reflect the clinically harsh nature of the proposed amendment by the ERG, we propose the following amendment: "8. The company also assumed long term treatment benefit post-	To reflect that the ERG's assumption to withdraw benefits post discontinuation reflect an extreme scenario and are not consistent with the expected residual benefits that have accumulated while patients are	Not a factual error

post-discontinuation efficacy in terms of the liver."	discontinuation in the liver model. The ERG removed this assumption as no evidence was provided of post-discontinuation efficacy in terms of the liver**; this, however, is an extreme clinical scenario because it does not reflect the reduction in the accumulation of fats in the liver while on metreleptin treatment and the associated long-term risk reduction in liver related complications.**"	on metreleptin, slowing disease progression.	
Section 1.11, Page 25: "9. The company model also assumed that 50% of the QoL treatment differential between metreleptin and SoC (assumed to cover issues such as hyperphagia, ability to perform work/schoolwork, physical appearance and PCOS) were maintained after discontinuation from metreleptin for patients and carers over the patient's remaining lifetime. No evidence was represented demonstrating a continued treatment effect in terms of hyperphagia, ability to perform work/schoolwork, physical appearance and PCOS after discontinuation and therefore this assumption was removed by the ERG."	To reflect the extreme nature of the proposed amendment by the ERG, we propose the following amendment: "9. The company model …. No evidence was represented demonstrating a continued treatment effect in terms of hyperphagia, ability to perform work/schoolwork, physical appearance and PCOS after discontinuation and therefore this assumption was removed by the ERG**. This, however, is an extreme clinical scenario because it does not reflect slowing of disease progression achieved while patients receive metreleptin treatment and the associated long-term risk reduction achieved via improvements in hyperphagia, ability to perform**	To reflect that the ERG's assumption to withdraw benefits post discontinuation reflect an extreme clinical scenario and are not consistent with the expected residual benefits that have accumulated while patients are on metreleptin, slowing disease progression.	Not a factual error

	work/schoolwork, physical appearance and PCOS."		

Issue 4 Surrogate outcome: ALT/AST

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.2, Page 154: "The ITC of ALT/AST data used to adjust transition probabilities for patients taking metreleptin in the company scenario analysis was based on the PL overall group but used the PL subgroup baseline values. This was corrected to use the baseline values from the PL overall group for consistency"	Given that the calculation of RR for the liver model already uses the PL overall group ALT/AST change, we propose removing the quoted sentence on page 154 as the change has no impact on the cost-effectiveness calculations or results.	The ALT/AST data used to calculate the RR for the liver model already uses the PL overall group data. The values adjusted by the ERG were not used directly in the calculation of the RR. Change required for accuracy and clarity.	Reference to this issue has been removed

Issue 5 PAS discount

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Whilst the PAS discount level has been marked as Commercial in Confidence (CiC), the prices per vial with PAS discount applied have not	The prices per vial following the PAS discount should also be marked as CiC, as follows:	PAS discount is commercial in confidential.	The missing CiC Mark-up has been added to the amended report.

been marked up appropriately on page 138: "Metreleptin is available in three vial sizes for injection for the following list prices per pack of 30 vials: 10 mg for £70,050, 5 mg for £35,025, and 2.5 mg for £17,512.50. A PAS discount of [redacted] is applied to these list prices, which gives the following per vial cost prices that are applied in the model: £[redacted] per 10 mg vial, £[redacted] per 5 mg vial, and £[redacted] per 2.5 mg vial."	"Metreleptin is available in three vial sizes for injection for the following list prices per pack of 30 vials: 10 mg for £70,050, 5 mg for £35,025, and 2.5 mg for £17,512.50. A PAS discount of [redacted] is applied to these list prices, which gives the following per vial cost prices that are applied in the model: [redacted] per 10 mg vial, [redacted] per 5 mg vial, and [redacted] per 2.5 mg vial."		

Issue 6 Surrogate outcome: triglycerides

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The following statement in section 5.3.3 (p137) of the ERG report, it is stated: "The arguments mentioned are all based on HbA1c and triglycerides, which control the probability of organ complications in the sub-models."	The following amendments to the text are proposed to this statement: "The arguments mentioned are all based on HbA1c and triglycerides. HbA1c ~~which~~ controls the probability of organ complications in the cardiovascular, renal, retinopathy and neuropathy sub-models."	Elevated triglycerides are known factors for cardiovascular complications. However, due to lack of data in the literature, the transition probabilities were not adjusted based on triglycerides. As recognised by the ERG, the current transition probabilities are expected to be an underestimate where hypertriglyceridemia contributes to the risk of a complication, such as cardiovascular disease (page 125, ERG Report. As such, this statement	The suggested wording change has been made.

		is mis-leading as it indicates triglycerides impact the probability of organ complications in the model, which is incorrect.	

Issue 7 Discontinuation rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
As part of the responses to the ERG questions, Amyrt had provided alternative discontinuation rates. These rates were obtained from previous submission materials and "summarised in section 4.15 of the previous FED". Section 4.15 of the previous FED provides detail about the derivation of the discontinuation rates. The following statement in section 5.3.3.7, p137 is misleading: "Given that these provide long-term estimates of discontinuation and show a plausible trend in discontinuation, with larger discontinuation in the first years, followed by lower discontinuation in the long-term, the ERG prefers to use these estimates in their base-case, despite little information being provided about their source."	The following amendments to the text are proposed: "Given that these provide long-term estimates of discontinuation and show a plausible trend in discontinuation, with larger discontinuation in the first years, followed by lower discontinuation in the long-term, the ERG prefers to use these estimates in their base-case. ~~despite little information being provided about their source.~~"	The source of these values is available through previous submissions of evidence and has been previously critiqued and agreed upon by the Committee. As such, the last part of this statement is incorrect and should be removed.	The ERG has removed the requested phrase.

Issue 8 Budget impact analysis

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 162-163

Calculation of medicine acquisition costs per patient per annum</td>
<td>The updated medicine acquisition costs per patient annum should be updated to [redacted]</td>
<td>Amyrt has identified that there is an inconsistency between the proportion of patients receiving each vial size values reported in the CS compared to those used in the analysis. The CS refers to a previous version of EAP data from 2017 but in the analysis the updated 2018 EAP data was applied. The value [redacted] was calculated using all three vial sizes but using updated 2018 values for the proportion of EAP patients receiving each vial size. The proportion of EAP patients receiving each vial size was multiplied by the PAS price per vial to give an average daily cost and further multiplied by 365.25 to give the medicine acquisition costs per patient annum. As such, this should be applied in the ERG's revised budget impact analysis.
<table>
<tr><th></th><th>Proportion of EAP patients receiving each vial size</th><th>PAS price per vial</th></tr>
<tr><td>5.8 mg vial (up to a 5 mg dose)</td><td>13.04% (n=[redacted]</td><td>[redacted]</td></tr>
<tr><td>11.3 mg vial (up to a 10 mg dose)</td><td>60.87% (n=[redacted]</td><td>[redacted]</td></tr>
<tr><td>3 mg vial (up to a 2.5 mg dose)</td><td>26.09% (n=[redacted])</td><td>[redacted]</td></tr>
<tr><td colspan="3">Abbreviations: EAP, Expanded access programme; mg, Milligram; n, Number</td></tr>
</table>
</td>
<td>The ERG have updated their analysis with the value of [redacted] as requested</td>
</tr>
</table>

Issue 9 NIH follow-up study inclusion in clinical effectiveness section of the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 9.3.2, page 170: "The study details and results for the NIH follow-up study and the GL/PL natural history study, which were used to inform the ITC and the cost effectiveness model, were not included in the clinical effectiveness section of the CS."	Remove the statement.	The study details for the GL/PL Natural History study and the NIH follow-up were provided in the clinical effectiveness section of the company submission (see Section 9.8.1, CS) and associated references provided in the reference pack. The NIH Follow-up study is formed of the patients in the NIH studies 991265/20010769, and the results from these studies are also provided in the clinical effectiveness section of the company submission (see section 9.6.1.1, CS).	The ERG recognises that some study details and baseline characteristics, for the NIH follow-up study and the GL/PL natural history study, were included in the clinical effectiveness section of the CS. However, whilst study reports were provided, the clinical effectiveness section of the CS does not include results for these studies; section 9.8.1 includes results for the ITC analysis, but not for the individual studies which informed this analysis, and section 9.6.1.1 includes results for the NIH studies 991265/20010769, but not the follow-up study. The text has been amended to indicate that results, but not study details, were missing from the clinical effectiveness section of the CS.

Issue 10 Addenbrooke's EAP results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, Page 16 (1st paragraph):	The text should be updated as follows:	There is no time point mentioned in this sentence, and we have	This error has been corrected.

“For example, for GL patients there was a change from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke’s EAP)”	"For example, for GL patients there was a change from 6.4 to ~~4.1 (about -2.3) mmol/l~~ 4.6 mmol/l and in patients with both baseline and Month 12 data the reduction was -3.5 mmol/l (Addenbrooke’s EAP)"	assumed the intention is to report changes at Month 12 compared to baseline. As such, the data does not correspond to the Month 12 data reported in Table 23 of the CS; instead the Month 36 value of 4.1 mmol/l is reported here. The Month 12 triglyceride value in the Addenbrooke’s EAP was 4.6 mmol/l and therefore the text should be updated. To calculate the absolute change in triglycerides from baseline to month 12 for generalised lipodystrophy (GL) patients, an analysis was provided in Table 7 in the response to ERG clarification questions for patients who have data available at both baseline and month 12. The value reported was -3.5 mmol/l and should be used when comparing data at different time points.	
Section 4.2.4.1, Page 63 (5th paragraph): “e.g. for GL patients there is a change from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke’s EAP)”	The text should be updated as follows: “e.g. for GL patients there is a change from 6.4 to ~~4.1 (about -2.3) mmol/l~~ 4.6 mmol/l and in patients with both baseline and Month 12 data the reduction is -3.5 mmol/l (Addenbrooke’s EAP)”		

Issue 11 Generalisability of NIH studies 991265/20010769 and NIH follow-up results to UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.5, Page 16 (1st line): “There is also some doubt as to the applicability of the NIH follow-up study to UK clinical practice.”	Remove this statement.	As part of the original submission, it was concluded at the FED stage that, regarding NIH 991265/20010769 study, the NIH follow-up and FHA101, that “Only 1	This is a matter of opinion and not a factual error.

Section 4.2.4.1, Page 63 (5th paragraph): "If the Addenbrooke's EAP patients have similar baseline characteristics to the NIH 991265/20010769 study and given that they have been obtained from the UK, then serious doubt must be cast on the representativeness of the NIH follow-up study results, most of the patients of whom come from the NIH 991265/20010769 study, to the UK setting."	Remove this statement. If retained, the statement should be updated to reflect clinical expert opinion as per the Final Evaluation Document (FED).	patient in these studies was recruited from the UK, but the clinical experts confirmed that the trial populations were generalisable to patients seen in clinical practice in England."(8) As such, these conclusions are no longer relevant and should be removed.	The comparison between Addenbrooke's EAP data and NIH follow-up results is new to this submission and, as such, is not covered by clinical expert opinion as per the Final Evaluation Document (FED).

Issue 12 Comparability of Addenbrooke's EAP PL subgroup to the licensed indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.10, Page 23 (4th paragraph), Section 4.6.3, Page 103 (3rd paragraph) and Section 9.4, Page 172 (3rd paragraph): "The CS indicates that the company considers that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is the PL population most considered to best reflect the licensed indication. However, this definition differs from that provided for the PL subgroup population in the Addenbrooke's EAP (baseline leptin	The company believes that this is misleading and should be updated as follows: "The CS indicates that the company considers that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) based on NIH studies 991265/20010769, is a PL population reflective of the licensed indication. ~~However, this definition differs from that provided for the~~ Leptin cut-offs were part of the PL subgroup definition in NIH studies	The PL subgroup in NIH studies 991265/20010769 is considered to be reflective of the licensed indication. Leptin cut-offs were part of the PL subgroup definition, through the inclusion criteria for NIH studies 991265/20010769, as noted in Table 14 of the CS: 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	Wording changes have been made, in the amended report, to reflect the use of leptin levels in the inclusion criteria of the NIH studies 991265/20010769.

<12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L).”	991265/20010769, through the study inclusion criteria. Therefore, the PL subgroup definition used in the Addenbrooke’s EAP (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is comparable to the PL subgroup in NIH studies 991265/20010769 and reflective of the licensed indication.”	NIH 991265: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males. Therefore, the PL subgroup in the Addenbrooke’s EAP is comparable to the PL subgroup in NIH studies 991265/20010769 and reflective of the licensed indication.	
Section 2.3, Page 31 (last paragraph): “The CS notes that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) is the PL population most considered to best reflect the licensed indication. However, this definition differs from that provided for the PL subgroup population in the Addenbrooke’s EAP (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L), given in Table 23 of the CS.”	The company believes that this is misleading and should be updated as follows: “The CS notes that the PL subgroup population (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) based on NIH studies 991265/20010769 is a PL population reflective of the licensed indication. ~~However, this definition differs from that provided for the~~ Leptin cut-offs were part of the PL subgroup definition in NIH studies 991265/20010769, through the study inclusion criteria. Therefore, the PL subgroup definition used in the Addenbrooke’s EAP (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L, given in Table 23 of the CS) is comparable to the PL subgroup in NIH studies 991265/20010769 and reflective of the licensed indication.”		Wording changes have been made, in the amended report, to reflect the use of leptin levels in the inclusion criteria of the NIH studies 991265/20010769.

Issue 13 Metreleptin survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.10, Page 23 (3rd paragraph) and Section 9.4, Page 172 (1st paragraph): "Furthermore, even after adjustment (and using several different adjustment methods), survival was worse with metreleptin, albeit not statistically significantly."	The company believes that this is misleading and should be updated as follows: "Furthermore, even after adjustment (and using several different adjustment methods), there was no statistically significant differences between metreleptin and supportive care, in terms of survival."	As there was no statistical significance observed using any adjustment methodology, no conclusions can be drawn as to survival being 'worse' with metreleptin.	This is a matter of opinion, in respect of wording, and not a factual error. The ERG has not stated that any conclusions can be drawn as to survival being 'worse' with metreleptin.

Issue 14 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.4, Page 14 (3rd bullet): "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: 46 to -8.6, p<0.001) in the PL subgroup excluding the one outlying noncompliant patient."	To update the text as follows: "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: ~~-46 to -8.6,~~ -49.6 to -25.2, p<0.001) in the PL subgroup excluding the one outlying noncompliant patient."	Typographical error – data input inaccurately.	This error has been corrected.
Section 1.10, Page 23 (last paragraph):	To update the text as follows:	Typographical error – data input inaccurately.	This error has been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The PL subgroup represents a subgroup of the PL overall patients who have at least % hbA1c level at baseline."	"The PL subgroup represents a subgroup of the PL overall patients who have at least ~~% hbA1c~~ 6.5% HbA1c level at baseline."		
Section 4.2.1, Page 49 (last paragraph): "The NIH991265/20010769 study (Table 4.4) included a much higher proportion of participants with GL, 66/107 (62%) than the FH101 study"	To update the text as follows: "The NIH991265/20010769 study (Table 4.4) included a much higher proportion of participants with GL, 66/107 (62%) than the ~~FH101~~ FHA101 study"	Typographical error – correct study name is FHA101.	This error has been corrected.
Table 4.4, Page 56: "PL (N=1)"	To update the text as follows: "PL ~~(N=1)~~ (N=41)"	Typographical error – data input inaccurately.	This error has been corrected.
Table 4.5, Page 57: "Baseline characteristics for study FH101, reproduced from Table 17, CS"	To update the text as follows: "Baseline characteristics for study ~~FH101~~ FHA101, reproduced from Table 17, CS"	Typographical error – correct study name is FHA101.	This error has been corrected.
Table 4.7, Page 60:	To update the text as follows: "Elevated ALT[c,d]: ~~48 (21.7) 26 (33.8) 22 (15.3)~~ 24 (27.6) 11 (37.9) 13 (22.4)" "Elevated AST[c,d] : ~~26 (12.3) 13 (17.1) 13 (9.6)~~ 11 (12.9) 6 (20.7) 5 (8.9)"	Typographical error – data input inaccurately. Proportion of patients with elevated ALT and AST have been updated to reflect patients' status at baseline as opposed to laboratory results closest to index date.	These errors have been corrected.
Table 4.8, Page 61:	To update the text as follows:	Typographical error – data input inaccurately.	These errors have been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	"GL patients of Native American race: ~~1~~ 1 (1.6)" "GL patients ≥20 years: 19 ~~(38.0)~~ (28.0)"		
Section 4.2.4.1, Page 62: "The corresponding values, for % change in triglyceride levels, were -32.1% (95% CI: -51.0%, -13.2%) for GL patients, -37.4% (95% CI: -57.2%, -8.6%) for the PL subgroup and -20.8% (95% CI: -51.0%, -13.2%) for all PL patients."	To update the text as follows: "The corresponding values, for % change in triglyceride levels, were -32.1% (95% CI: -51.0%, -13.2%) for GL patients, -37.4% (95% CI: ~~-57.2%, -8.6%~~ -49.6% to -25.2%) for the PL subgroup and -20.8% (95% CI: ~~-51.0%, -13.2%~~ -37.1% to -4.6%) for all PL patients."	Typographical error – data input inaccurately.	These errors have been corrected.
Section 4.2.4.1, Page 63 (1st paragraph): "The smaller, single arm metreleptin treatment study, FH101"	To update the text as follows: "The smaller, single arm metreleptin treatment study, ~~FH101~~ FHA101"	Typographical error – correct study name is FHA101.	This error has been corrected.
Table 4.9, Page 65:	To update the text as follows: Change row 20 of Table 4.9, relating to the percent change from baseline at Month 12 in triglycerides using LOCF (FAS population, excluding outlier patient) PL subgroup: 95% CI: ~~-57.2%, -8.6%~~ -49.6% to -25.2%	Typographical error – data input inaccurately.	These errors have been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
	PL overall: 95% CI: ~~-51.0%, -13.2%~~ -37.1% to -4.6%		
Table 4.11, Pages 70-72:	To update the text as follows: "Table 4.11 Glycaemic control and lipid metabolism, results from ~~FH101~~ FHA101 study" Remove the second to last row of Table 4.11 on page 72 which corresponds to ≥2% actual decrease in HbA1c or ≥40% decrease in triglycerides: Month 12 value, LOCF: Mean (SD) for GL, PL subgroup and PL overall patients.	Typographical error – correct study name is FHA101 and data input inaccurately.	This error has been corrected.
Section 4.2.4.1, Page 76 (2nd paragraph): "Similar results were reported for the smaller FH101 study in Appendix 10, CS (see Table 4.15)"	To update the text as follows: "Similar results were reported for the smaller ~~FH101~~ FHA101 study in Appendix 10, CS (see Table 4.15)"	Typographical error – correct study name is FHA101.	This error has been corrected.
Table 4.15, Page 77: "Hepatic enzymes results from FH101 study"	To update the text as follows: "Hepatic enzymes results from ~~FH101~~ FHA101 study"	Typographical error – correct study name is FHA101.	This error has been corrected.
Section 4.2.4.1, Page 80: "19/46 (41%) of GL patients and 4/25 (16%) PL patients were classified as having experienced an improvement in their kidney	To update the text as follows: "~~19/46 (41%)~~ 16/46 (35%) of GL patients and ~~4/25 (16%)~~ 3/25 (12%) PL patients were classified as having experienced an improvement in their	Typographical error – data input inaccurately.	These errors have been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
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"	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%)~~ eleven (50%) had emergent kidney abnormalities after metreleptin initiation, and ~~4/19 (21%)~~ 9/19 (47%) of PL patients who had no evidence of ~~heart~~ kidney abnormalities before treatment had emergent abnormalities after metreleptin initiation."		
Section 4.2.4.1, Page 80: "Using the same approach, of the 79 GL patients who did not have heart damage at baseline 27 (34%)	To update the text as follows: "Using the same approach, of the ~~79~~ 74 GL patients who did not have heart damage at baseline ~~27 (34%)~~	Typographical error – data input inaccurately.	These errors have been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
developed heart damage during follow-up and 34/140 (24%) of PL patients who did not have heart damage at baseline developed damage during follow-up."	22 (30%) developed heart damage during follow-up and ~~34/140 (24%)~~ 33/139 (24%) of PL patients who did not have heart damage at baseline developed damage during follow-up."		
Section 4.2.4.1, Page 82: "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."	To update the text as follows: "With respect to lipid-lowering medication, 19/35 (54.3%) of GL patients and 16/38 ~~(68.2%)~~ (42.1%) of PL patients were able to discontinue lipid lowering medications."	Typographical error – data input inaccurately.	This error has been corrected.
Section 4.2.4.1, Page 83: "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	To update the text as follows: "Over the whole observation period, ~~2/15 (13.3%)~~ 16/48 (33.3%) of female GL patients and ~~15/41 (36.6%)~~ 40/112 (35.7%) 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~~ 32 female GL patients who did not have reproductive dysfunction at baseline,	Typographical error – data has been copied across from the original ERG report published in April 2018, which used data from 178 of 230 GL/PL Natural History study patients.	These errors have been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
19/26 (73.1%) of female PL patients who did not have reproductive dysfunction at baseline developed problems during follow-up."	~~nine (69.2%)~~ 12 (37.5%) developed reproductive dysfunction during follow-up and ~~19/26 (73.1%)~~ 24/72 (33.3%) of female PL patients who did not have reproductive dysfunction at baseline developed problems during follow-up."		
Table 4.20, Page 92: "On-study deaths, study FH101 (safety analysis set)"	To update the text as follows: "On-study deaths, study ~~FH101~~ FHA101 (safety analysis set)"	Typographical error – correct study name is FHA101.	This error has been corrected.
Table 4.22, Page 93-95:	To update the text as follows: New table in Appendix 1, Table 1	Typographical error – data has been copied across from the original ERG report published in April 2018, which used data from 178 of 230 GL/PL Natural History study patients.	Corrected – the ERG have replaced Table 4.22 with the one kindly provided by the company.
Section 5.5, Page 152 (4th paragraph) "The PL subgroup represents a subgroup of the PL overall patients who have at least % hbA1c level at baseline."	To update the text as follows: "The PL subgroup represents a subgroup of the PL overall patients who have at least ~~% hbA1c~~ 6.5% HbA1c level at baseline."	Typographical error – data input inaccurately.	This error has been corrected.

References

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6. Porterhouse Insights. Lipodystrophy caregiver disease burden survey. 2020.

7. Brown RJ, Valencia A, Startzell M, Cochran E, Walter PJ, Garraffo HM, et al. Metreleptin-mediated improvements in insulin sensitivity are independent of food intake in humans with lipodystrophy [Internet]. American Society for Clinical Investigation; 2018 [cited 2020 Jun 10]. Available from: https://www.jci.org/articles/view/95476/pdf

8. NICE. Final evaluation document: Metreleptin for treating lipodystrophy. 2019.

Appendix 1 – Corrected tables from ERG report

Table 1 is corrected from Table 4.22 and is presented below.

Table 1: Mortality and cause of death data from the GL/PL Natural History Study

	All Patients (n=230)	GL Patients (n=81)	PL Patients (n=149)
Years from first GL/PL symptoms to end of observation period*			
Mean (SD)	14.5 (12.5)	12.6 (9.5)	15.5 (13.7)
Median (IQR)	11.1 (4.8, 20.3)	10.7 (5.5, 17.0)	11.6 (4.8, 21.7)
Years from first GL/PL symptoms to diagnosis			
Mean (SD)	6.9 (10.8)	3.1 (6.4)	9.0 (12.0)
Median (IQR)	1.4 (0.0, 10.0)	0.3 (0.0, 1.6)	4.0 (0.0, 14.3)
Patients still alive, n (%)			
Yes	180 (78.3)	54 (66.7)	126 (84.6)
No	18 (7.8)	10 (12.3)	8 (5.4)
Unknown	32 (13.9)	17 (21.0)	15 (10.1)
Years from first GL/PL symptoms to death**			
Kaplan-Meier Mean (SE)	47.6 (2.0)	29.4 (1.5)	51.6 (1.9)
Median (IQR)	56.3 (34.5, NR)	31.7 (26.4, NR)	56.3 (56.3, NR)
Patients who died, n	18	10	8
Age at first GL/PL symptoms			
Mean (SD)	22.1 (20.3)	13.5 (19.5)	32.9 (16.6)
Median (IQR)	16.9 (4.0, 30.6)	5.3 (0.3, 15.0)	29.6 (22.4, 43.0)
Age at death			
Mean (SD)	42.3 (18.4)	33.8 (17.0)	52.9 (14.7)
Median (IQR)	37.4 (30.4, 60.2)	30.9 (18.7, 44.5)	56.5 (37.4, 66.0)
Death related to lipodystrophy, n (%)			
Yes	11 (61.1)	8 (80.0)	3 (37.5)
No	0	0	0
Unknown	7 (38.9)	2 (20.0)	5 (62.5)
Patients who died, n	18	10	8
Cause of death reported,$ n (%)	14 (77.8)	10 (100.0)	4 (50.0)
Method of assessing cause of death, n (%)			
Per practice health records	5 (27.8)	2 (20.0)	3 (37.5)
Per physician recollection	5 (27.8)	4 (40.0)	1 (12.5)
From death certificate	4 (22.2)	3 (30.0)	1 (12.5)
Not confirmed	0	0	0
Unknown	4 (22.2)	1 (10.0)	3 (37.5)
Potential contributing factors, n (%)			
Bone marrow/hematologic abnormalities	1 (5.6)	2 (20.0)	0
Cancer	0	4 (40.0)	0
Cardiovascular event	6 (33.3)	3 (30.0)	3 (37.5)
Cerebrovascular disease	3 (16.7)	1 (10.0)	2 (25.0)
Immunosuppression	1 (5.6)	1 (10.0)	0
Infection (viral)	0	0	0
Infection (bacterial)	3 (16.7)	3 (30.0)	0
Liver disease	4 (22.2)	3 (30.0)	1 (12.5)
Pancreatitis	2 (11.1)	2 (20.0)	0
Pneumonia	2 (11.1)	2 (20.0)	0
Renal failure	2 (11.1)	1 (10.0)	1 (12.5)

	All Patients (n=230)	GL Patients (n=81)	PL Patients (n=149)
Sepsis	1 (5.6)	1 (10.0)	0
Unknown	5 (27.8)	1 (10.0)	4 (50.0)
Other[$$]	1 (5.6)	1 (10.0)	0
Location where patient died, n (%)			
At home	1 (5.6)	1 (10.0)	0
At the hospital	11 (61.1)	7 (70.0)	4 (50.0)
Unknown	5 (27.8)	1 (10.0)	4 (50.0)
Other[$$$]	1 (5.6)	1 (10.0)	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, polycythaemia, acanthosis nigricans, hypertriglyceridemia), myocardial infarction, possible cardiac episode, probable end stage liver disease, and stroke
$$Other potential contributing factors of death included mentions of pancytopenia, steatohepatitis, and chronic renal insufficiency
$$$ Other locations where a patient died included a hotel

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

ID861 Metreleptin for treating lipodystrophy

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
The clinical use of metreleptin in consideration of its current markeing authorisation		
1. Population that would be eligible for treatment	• Metreleptin was granted a marketing authorisation under exceptional circumstances by the European Medicines Agency (EMA) on the 29 July 2018. Metreleptin (Myalepta) is indicated, as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: o with confirmed congenital generalised lipodystrophy (CGL; called Berardinelli-Seip syndrome) or acquired generalised lipodystrophy (AGL; called Lawrence syndrome) in adults and children two years of age and above o with confirmed familial partial lipodystrophy (FPL) or acquired partial lipodystrophy (APL; called Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control • From the submission it is not clear what criteria will be used to determine which patients with partial lipodystrophy will receive metreleptin treatment in clinical practice. • The company's main trial NIH study included generalised lipodystrophy (GL) and partial lipodystrophy (PL) populations, and among the PL population, a PL subgroup who had similar metabolic disturbances to those seen in patients with GL (baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L) was defined. The company considers that this PL subgroup represents a more severe group compared with the overall PL population as they are more at risk of organ damage and best reflects the licensed indication. • The company used the overall PL population for the indirect treatment comparison (ITC) which aimed to establish the comparative effectiveness of	• The technical team agrees with the ERG that the treatment decision should be clear and reflected clearly in the model parameters, otherwise it is unclear to what extent the model results could reflect those PL patients who will have metreleptin in practice. • Clinical advice would be appreciated regarding which PL patients would be eligible for metreleptin treatment in clinical practice in the UK and what criteria would be used. • See related questions in paragraph I below.

	metrelptin relative to supportive care. However, the model inputs for the economic analysis were based on the PL subgroup, including baseline levels of metabolic surrogates and changes from baseline of HbA1c. • This PL subgroup definition in NIH study also differs from the PL subgroup population in the Addenbrooke's Early Access Programme (EAP) (baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L). The EAP has run for more than 10 years and was used by the company for baseline patient distribution in the model because the prevalence of GL and PL observed in the EAP was assumed to be representative of eligible patients in the UK.	
Issues related to the clinical evidence		
2. Representativeness of studies used to inform clinical effectiveness of metreleptin	• The main clinical trials providing clinical evidence are the following: o NIH 991265/20010769/NIH follow-up study: open-label, single-arm study to evaluate disease status prior to metreleptin initiation and outcomes following therapy (n=112, GL=68, PL=44); co-primary outcome: actual change from baseline in HbA1c at Month 12, and percent change from baseline in fasting serum triglycerides at Month 12; mean follow-up time: 8.8. years for GL and 7.7 years for PL patients o The GL/PL natural history study: non-interventional, observational study (n=178, GL=56, PL=122); primary outcome: continuous variables described in terms of means, standard deviations, and medians; secondary outcome: time to first organ damage and time to progression; mean follow-up time: 9.5 years for GL and 6.5 years for PL patients o The company also presented data from EAP: early access programme assessing the burden of disease and performance of metreleptin in lipodystrophy patients (n = [redacted], GL= [redacted], PL= [redacted]); the study has run for over 10 years; follow-up time when results of outcomes were reported: up to 36 months • The committee previously came to natural the conclusion that it had concerns about the generalisability of the GL/PL history study population to people with	• There is no head-to-head comparison between metreleptin and supportive care, and the NIH study and GL/PL natural study were used in the ITC to establish the relative treatment effect of metreleptin.The study with the population that represents those that will be seen in the NHS is be preferred for the comparison. • The technical team agrees with the ERG's concern regarding the representativeness of NIH follow-up study. Stakeholders' opinion on whether the population of NIH follow up study is representative of those seen

	LD in England. The clinical experts stated that it was not clear whether the population was generalisable to patients in England (see section 4.9 in ECD). • With the availability of EAP data in the current submission, the ERG raised concerns about the generalisability of NIH follow-up study and whether the treatment effect of metreleption observed in the NIH study could be realised in UK practice. • This is because the ERG noted some discrepancies in the effects of metreleptin treatment (particularly with respect to changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a 12 months change from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke's EAP) vs. -10.54 mmol/l (NIH follow-up). The ERG noted that the EAP figure is closer to that of the GL/PL Natural History study of -4.43 mmol/l. • The change in HbA1c at 12 months was also lower in the EAP than in the NIH follow-up study. For example, for all patients, it was -1.94% HbA1c in the NIH follow-up study vs. the highest value, which was -1.5 % HbA1c, for GL patients in the Addenbrooke's EAP data. • Given these discrepancies and the apparent worse HbA1c and triglyceride outcomes observed in the EAP patients, the ERG therefore recommend consideration of the performance of the ITC using data from the EAP, particularly for HbA1c and triglycerides.	in the UK and whether the ITC would be better informed by the EAP data will be appreciated. • See related questions in paragraph II below.
3. The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison	• There is no head-to-head trial between metreleptin and supportive care and the clinical effectiveness evidence mainly comes from the NIH follow up, which is a single arm study. • The company thefore performed an indirect treatment comparison (ITC) to estimate the relative difference in key clinical outcomes (change in HbA1c, triglycerides, ALT and AST from baseline to Month 12; incidence of pancreatitis, and all-cause mortality) between metreleptin and supportive care. Methodologies recommended by NICE DSU TSD17 were followed. • The ERG noted that only three baseline characteristics were adjusted for in the ITC, based on clinical opinion, namely, lipodystrophy type (GL or PL), gender and age at baseline. • The ERG was concerned with the selection of covaraites used in the ITC, because important prognosis variables such as baseline HbA1c, triglycerides,	• The technical team agrees with the ERG's concern about the selection of covarates included in the ITC and the limited number of covariates adjusted for. • Stakeholder's opinion is sought on whether the ITC would become more reliable and informative for decision making with the addition of other potential covaraites such as country, ethnicity,

	leptin levels, and baseline pancreatitis were not adjusted for in the analysis. The company argued that these factors were not confounding because they were not related to treatment allocation. It also stated that a sensitivity analysis using additional co-variates was explored, but this analysis was not feasible due to either small sample size or overfitting.	and important baseline prognosis factors such as HbA1C. • See related questions in paragraph III below.
4. Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD	• Only evidence with a short follow-up time (mostly limited to one-year) is available from the main trials of the company. • The ITC estimated the effects of metreleptin for no longer than 12-months, mainly on surrogate outcomes such as HbA1c, triglycerides, ALT/AST. • No evidence is available to support metreleptin's long-term treatment effect on clinically important outcomes such as organ damage of the liver, heart and kidneys, also on the important patient-perceived outcome of hyperphagia and quality of life. • The ERG noted that NIH follow-up study indicated that new incidences of hard clinical outcomes such as organ abnormalities (liver, kidney and heart) and female reproductive dysfunction continue to occur, in all categories of LD patient, on metreleptin treatment. • The ERG also noted that improvement in surrogate outcomes, such as HbA1c, 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). However, they are not, in themselves, evidence of treatment effect on long-term health outcomes. • The ERG highlighted that, where links between these surrogate outcomes and long-term health outcomes are generally accepted, the evidence underpinning such links was derived from populations very different from the LD population. • However, the 'post-metreleptin improvements' reported in the NIH follow-up study were frequently based on measures taken at one year and used the definitions based on changes in surrogate outcome measures; • Regarding metreleptin's long term treatment effect, uncertainties also exist in terms of the development of neutralising antibodies and the potential effects of that remain unclear. In NIH 991265/20010769 study 88% of people developed antibodies to metreleptin. Both attenuation (denoted by initial improvement and then decline of both HbA1c and triglyceride levels) and worsening	• The technical team noted the concerns of the ERG that there is little information about the long-term effects of metreleptin treatment, particularly in relation to patient-perceived (hyperphagia) and hard clinical outcomes (e.g. liver damage); • The ITC mainly estimated the effects of metreleptin on surrogate outcomes for < 12 months. The technical team would seek stakeholders' opinion on: • The long-term treatment effect of metreleptin on clinical outcomes while being on treatment; • whether the general surrogate relationship between metabolic measures such as HbA1c and hard clinical outcomes such as liver and heart diseases is the same in people with lipodystrophy, and

	(denoted by decline from baseline in both HbA1c and triglycerides) of metreleptin effect were reported in patients with PL and GL, both with and without neutralising antidrug antibodies. These cases raised concern that development of neutralising antibodies to metreleptin could impair metabolic control and immune function.	• the impact of neutralising antibodies to metreleptin on the treatment's effect on metabolic outcomes in the long term. • See related questions in paragraph IV below.
5. Discontinuation rate of metreleptin treatment	• The company assumes in its base-case that patients will only stop treatment for non-compliance, associated with discontinuation rates of 1.5% and 3.86% for GL and PL from the NIH trials. • The ERG did not agree with the company choice that only discontinuation due to non-compliance should be included in the modelled discontinuation. • During clarification the company provided final evaluation decision discontinuation rates of 8.93% in year 1, 5.63% in years 2-9 and 2.04% in years 10 onwards. This reflects the discontinuation observed in the first year of the NIH trial closer and the decline in discontinuation over time seems plausible. • The ERG used these rates in their base-case because this data provides long-term estimates of discontinuation.	• The technical team agrees with the ERG that compliance should not be the only reason for discontinuation of metreleptin treatment. It prefers the ERG's base-case, using time-based discontinuation rates. • See related questions in paragraph V below.
Issues related to cost-effectiveness: evidence/assumptions used to inform the company's model parameters		
6. Baseline transition probabilities and pathway through organ sub-models	• The company presented a de-novo individual patient level simulation model. The model consists of six Markov sub-models simulating the progression of disease on distinct organ systems affected by lipodystrophy including: pancreas, liver disease, cardiovascular disease, kidney, neuropathy and retinopathy. • Among the six sub-models, only the pancreatitis sub-model estimated risk of pancreatitis in each treatment group directly from the the ITC. • The liver baseline complications were derived from the NICE non-alcoholic fatty liver disease (NAFLD) guideline model, and risk reduction associated with metreleptin in comparison with supportive care was estimated from the Delphi panel study conducted by the company (with reduction in AST/ALT levels estimated from the ITC used in a scenario).	• The technical team agrees with the ERG's concerns about the generability of the assumption that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but different aetiology. Stakeholders' views on

	• Baseline transition probabilities for the liver, cardiovascular, kidney, neuropathy and retinopathy sub-models were obtained from the literature. Diabetes-related baseline transition probabilities have been used for the diabetes-related complications, i.e. cardiovascular, kidney disease, neuropathy and retinopathy. • HbA1c was used to adjust the risk of organ complications and account for the reduction in risk of organ complications associated with metreleptin in these four submodels. Since the ITC for HbA1c could not be estimated separately in GL and PL patients, the naïve change in HbA1c from baseline from the NIH studies was used to determine efficacy. • As supported by clinical experts, the company's model assumpted that GL and PL patients are at higher risk of: o Pancreatitis, especially those who raised triclycerides level. o non-alcoholic fatty liver disease (NAFLD) (specifically non-alcoholic steatohepatitis), as a result of ectopic fat deposition, leading to the development of complications such as cirrhosis and hepatic cell carcinoma; o cardiovascular disease, particularly those with hypertriglyceridaemia and diabetes (i.e. elevated HbA1c); and kidney disease, neuropathic disease, and etinopathy, especially those with diabetes (i.e. elevated HbA1c); • The updated model structure submitted by the company includes suggestions by the NICE committee from previous evaluation meetings to account for organ complications in the progression of LD. However, the ERG pointed out that it remains predicated upon the assumption that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but different aetiology. This is therefore an area of considerable uncertainty. It is unclear to what extent these input values are generalisable to lipodystrophy patients. • The ERG also commented that it is uncertain to what extent will lipodystrophy patients follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions.	whether this assumption is clinically plausible would be needed; • Stakeholders' opinions on whether it is appropriate to use HbA1c to adjust the risk of organ compalictions in patients with LD in the the 4 sub-models (cardiovascular, kidney disease, neuropathy and retinopathy) will also be appreciated. • See related questions in paragraph VI below.
7. Metreleptin's continued treatment effect	• The change in HbA1c from baseline at 12 months in patients treated with metreleptin was used to adjust the baseline transition probabilities to generate probabilities for the metreleptin cohort in the cardiovascular, kidney,	• The technical team agrees with the ERG's concerns that because of the

on HbA1c post-discontinuation	neuropathy and retinopathy sub-models. Naïve change from baseline data from the NIH studies was utilised rather than comparative data for change in HbA1c from baseline. • Each patient entered the model with a baseline HbA1c level (based on the NIH study) and gender and types of lipodystrophy (GL/PL). In the first cycle, patients receiving metreleptin experienced the full reduction in their HbA1c levels based on the change from baseline to 12 months observed in the NIH study. • After that in every cycle all patients in the model received an annual increase in HbA1c of 0.15%, regardless of whether they are on treatment with metreleptin, have discontinued from metreleptin or are receiving SC --> discontinuation had no impact on efficacy in the four organ sub-models using HbA1c to determine transition probabilities. This is because patients were assumed to have received the full benefit of metreleptin in terms of HbA1c reduction in the 1st cycle and HbA1c rises at the same rate as patients taking supportive carethereafter. The model therefore also assumes that, post-discontinuation, the relative efficacy of metreleptin remains constant over the lifetime. This was done by the company in line with a previous NICE appraisal in diabetes TA315 intended to reflect disease progression in diabetes • The company argued that longer-term data has shown that HbA1c reductions observed with receiving metreleptin have been sustained for at least 48 months. • The ERG argued that the evidence was for patients on metreleptin for 48 months and no evidence was provided of the efficacy of metreleptin post-discontinuation. And the model assumes that the relative efficacy of metreleptin remains constant, over the lifetime. • Therefore the ERG considered this assumption unrealistic. Based on TA315, the ERG modelled a reversal of the treatment effect on HbAc1 in the cycle after discontinuation to remove this assumption of long term continued treatment effect post metreleptin discontinuation.	reduction in HbA1c due to metreleptin the average patient takes many years to reach the ceiling in either treatment group. • This assumption of continued post-discontinuation efficacy has a large impact on results. • There is no data on HbA1c levels post discontinuation from metreleptin, therefore the team prefers the ERG's base-case and considered that the assumption should be removed from the model. • It remains uncertain whether the relative treatment effect of metreleptin on HbA1c compared with supportive care would remain constant after the 1st cycle in the model. • There may be a scenario where only a proportion of patients in the model would receive an annual increase in HbA1c of 0.15% after the 1st cycle. • Stakeholders' opinions are sought in terms of metreleptin's partial continued treatment effect post-discontiuation given the lack of data in the body of

		evidence, for example, in terms of how much could be assumed and for how long. • See related questions in paragraph VII below.
8. Metreleptin's continued treatment effect on liver complications post discontinuation	• In the company's submission there is little evidence of the long-term effectiveness of metreleptin in patients continuing treatment, nor the residual of metreleptin's treatment effect post discontinuation; • Besides the assumed long-term continued efficacy in terms of HbA1c levels, the company also assumed long-term risk reduction in liver complications and partial lifetime QoL benefits for patients and carers after metreleptin discontinuation. • Specifically, liver benefits are maintained post discontinuation under the assumption that a short-term reduction in fatty deposits and accumulation in the liver will yield a longer-term benefit. However, no data was provided in the submission on these outcomes and the ERG removed this assumption as no evidence was provided of post-discontinuation efficacy in terms of the liver.	• The technical team agrees with the ERG that no evidence was presented regarding the post-discontinuation efficacy of metreleptin and therefore these assumptions could not be substantiated. • See related questions in paragraph VIII below.
9. Metreleptin's continued treatment effect on quality of life (utility differential) post-discontinuation and assumptions around additional utilities used in the model	• The company's model also accounted for the impact of metreleptin on lipodystrophy specific symptoms which were assumed not to be accounted for in the organ sub-models (e.g. hyperphagia, inability to work and impaired physical appearance). • It was modelled as a differential in utility between patients receiving metreleptin and standard of care (0.12 based on a discrete choice experiment (DCE) which estimated disutilities for lipodystrophy complications and symptoms valued by the general population). • A disutility due to caring was also modelled for carers of patients receiving standard of care. This disutility was estimated using the EQ-5D in a small group of carers of lipodystrophy patients. • The company assumed that if a patient discontinued from metreleptin, 50% of the 0.12 treatment differential and 50% of the benefit to carers was maintained post-discontinuation over the patient's remaining lifetime. • The ERG noted that the 50% of utility benefit maintained for patients over their lifetime in the model is associated with a lower incidence of the symptoms of hyperphagia, inability to work, polycystic ovary syndrome and impaired	• The technical team agrees with the ERG that no data for continued metreleptin effect after discontinuation was presented. Therefore it prefers the ERG's base-case which removed the partially continued utility differentials assumed in the model. • See related questions in paragraph IX below.

	physical appearance in patients taking metreleptin. However, no evidence has been provided that these issues are reduced once a patient discontinues from metreleptin compared to patients who only received SoC • The assumptions of 50% continued lifetime treatment effect over for patients and carers were removed from the ERG base-case model.	
10. Number of carers used in the model	• The company base-case assumed that each patient had carers. • The number of carers reported in the Lipodystrophy Caregiver Burden Survey data was 1.67 per patient. • However, the company's base-case used the average carer scenario (rounded value) and assumed 2 carers per patient. • The ERG corrected this in its base-case by using the average value of 1.67.	• The ERG's number is preferrable because it is more closely aligned to the carer survey.See related questions in paragraph X below.
Remaining uncertainties		
11. The DCE study and evidence used to inform utility values in the model	• The company presented a de-novo individual patient level simulation model. The model consists of six Markov sub-models simulating the progression of disease on distinct organ systems affected by lipodystrophy including: pancreas, liver disease, cardiovascular disease, kidney, neuropathy and retinopathy. • Data on disutilities related to organ complications used in the model are mostly obtained from the literature in non-lipodystrophy populations. • The ERG added that it is unclear how representative these are of lipodystrophy patients as these values were measured in different patient populations. • A few utilities which are specific to people with LD, including utility decrements for pancreatitis and other lipodystrophy specific symptoms (e.g. hyperphagia) were sourced from a DCE study (from the original submission), which estimated disutilities for lipodystrophy complications and were valued by general population samples in 6 countries including the UK. • The committee previously concluded before that the study was associated with substantial limitations. The ERG also flagged that it is unclear to what extent these input values are generalisable to lipodystrophy patients and therefore the utility estimates used in the model are subject to uncertainty.	• The technical team considered the issues around the generalisability of utility decrements from other populations and limitations in the study design of the lipodystrophy DCE study. • It recalled that the DCE study was associated with several issues before. • Given the concerns raised by the ERG and lack of alternative data, the best approach to modelling remains uncertain.

	• The ERG however concluded that no changes to the utility values or decrements assumed for patients can be made by the ERG in the base-case as no better alternatives are available.	

2 Questions for engagement

I. The clinical use of metreleptin in consideration of the current marketing authorisation: Population that would be eligible for treatment

1. Which patients with lipodystrophy would be eligible for metreleptin in clinical practice and what criteria would be used when it comes to the eligibility criteria?

2. The MA for the use of metreleptin in patients with partial lipodystrophy (PL) is not restrictive. Would you limit its use to a subgroup of patients and if so why? To your knowledge is there any consensus amongst UK experts treating patients with lipodystrophy in this?

3. Would you expect that the subgroup of people with PL (defined as HbA1c ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L) would have a different natural history from the overall PL population? Would you expect that the disease defined by the above characteristics wouldrespond differently to metreleptin? Do patients with lower concentrations of leptin follow a different course and would you expect their response to metreleptin to differ from that of the full PL population?

II. Clinical evidence: representativeness of studies used to inform clinical effectiveness of metreleptin

4. Are the populations in the main studies (the NIH study and the GL/PL natural history study) which were used to inform the indirect treatment comparison representative of those seen in UK clinical practice?

5. What is causing the discrepancy in the effects of metreleptin treatment noted (particularly with respect to changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a 12 months change in triglyceride levels from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke's EAP) vs. -10.54 mmol/l (NIH follow-up). Which treatment effect is more likely to be observed in future UK clinical practice?

6. Would different criteria be used in the future for patients when it comes to metreleptin treatment than those required for in the EAP and would a different response be expected? If yes, in what way?

III. The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison (ITC)

7. Limited number of covariates were adjusted for in the ITC conducted by the company, are those covariates (namely, age, gender and lipodystrophy type) the most important and relevant for baseline difference adjustment to predict the course of the disease? Would stakeholders expect to see the absolute change in HbA1c and triglyceride levels associated with metreleptin treatment vary with baseline HbA1c or triglyceride level?

8. Would it be appropriate to use the EAP (Early Access Programme) study, which includes only UK patients at Addenbrooke's Hospital, instead of the NIH study for the ITC?

IV. Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD

Only evidence with a short follow-up time (mostly limited to one-year) is available from the main trials of the company, and there is no evidence available to support metreleptin's long-term treatment effect on clinically important outcomes such as organ damage of the liver, heart and kidneys, or on the important patient-perceived outcome such as hyperphagia. There is also no evidence available on the long-term residual treatment effect of metreleptin post-discontinuation.

9. What is the stakeholder's view on the long term treatment effect of metreleptin on clinical outcomes such as organ abnormalities (liver, kidney and heart) and female reproductive dysfunction? Is there any reason that these abnormalities and dysfunction would not continue to occur at a rate consistent with future levels of HbA1c and triglycerides while patients are having metreleptin treatment in the longer term?

10. What is the stakeholder's view on the long term treatment effect of metreleptin on patient reported outcomes such as hyperphagia and quality of life?

11. There are case reports of neutralizing antibody limiting the effect of metreleptin. Would stakeholders expect that to be the case in a significant proportion of treated patients and what impact would be expected on outcomes such as HbA1c and triglycerides in the long term?

12. For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume? If yes, by what mechanism? If this is thought likely, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible? And how much?

13. Is there a correlation between surrogate outcomes such as HbA1c and clinical outcomes such as cardiovascular and kidney diseases in people with LD and is this the same as seen in other diseases, for example, diabetes?

V. Discontinuation rate of metreleptin treatment

14. What discontinuation rate on metreleptin treatment is likely to be seen in UK clinical practice?

15. Is a constant annual discontinuation rate of 1.50% for GL patients and 3.86% for PL patients from NIH study representative of what would happen in clinical practice? Alternatively is a declining rate of 8.93% in year 1 (which closely reflects the discontinuation observed in the first year of the NIH trial), and 5.63% in years 2-9 and 2.04% in years 10 onwards (representing the decline in discontinuation over time)more plausible?

VI. The model: baseline transition probabilities and pathway through organ sub-models

In the company's model, patient transitions between states of each of the sub-models were mostly determined by transition probabilities from the literature, in populations relevant to each sub-model condition, which were adjusted using surrogate outcomes such as HbA1c, AST\ALT to account for the reduction in risk of organ complications associated with metreleptin.

16. Is it appropriate to assume that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but caused by different underlying diseases, and therefore patients with lipodystrophy will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions but caused by different underlying disease states?

17. Can the stakeholders provide feedback on the extent to which these input values and transition probability estimates are generalisable to patients with lipodystrophy? Are the populations used to estimate transition probabilities generalisable for UK clinical practice?

18. Is it appropriate to use HbA1c or ALT/AST to adjust the transition probabilities and account for the reduction in risk of organ complications associated with metreleptin in sub-models?

VII. Metreleptin's continued treatment effect on HbA1c post-discontinuation

There is no evidence on metreleptin's continued treatment effect on outcomes including HbA1c levels, liver disease, and quality of life post discontinuation – data was not presented in the clinical section of the submission. In the company's model, the absolute change in HbA1c from baseline to 12 months associated with metreleptin was used to adjust the baseline transition probabilities to generate probabilities for the metreleptin cohort in the cardiovascular, kidney, neuropathy and retinopathy sub-models.

In the first cycle of the model, patients receiving metreleptin experienced the full reduction in their HbA1c levels observed at 12 months of NIH study. After that in every cycle all patients in the model received an annual increase in HbA1c of 0.15%, regardless of whether they are on treatment with metreleptin, have discontinued from metreleptin or are receiving SC. In other words, discontinuation of metreleptin was assumed to have no impact on its efficacy in the four organ sub-models using HbA1c to determine transition probabilities, because patients have received the full benefit of metreleptin in terms of HbA1c reduction and HbA1c rises at the same rate as patients taking supportive care from after the 1st cycle.

19. (1st part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?

20. Is it appropriate to assume that, post-discontinuation of metreleptin treatment, the relative efficacy of metreleptin compared with supportive care would remain constant over the life time, and the change in HbA1c level will be the same in the metreleptin and supportive care groups?

21. Would a scenario in which only a proportion of patients would experience the 0.15% increase in HbA1c after the 1st cycle be possible?

VIII. Metreleptin's continued treatment effect on liver complications post discontinuation

19. (2nd part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?

IX. Sources of utility values and assumptions around additional utilities used in the model

22. Is it appropriate to use utility values from the literature based on populations with disorders other than LD, on which the sub-models are based and apply them to LD populations at the same state in the model?

23. Is it appropriate to assume additional differential in utility (measure of QoL) between patients receiving metreleptin and standard of care (0.12 based on the DCE study) to account for changes in quality of life not captured by the health states in the sub-models? Similarly shoud there be a disutility due to the burden of caring in the models? If yes, is it appropriate to assume that some of these additional utilitities would be maintained post-discontinuation (over the patient's lifetime) and why?

X. Number of carers

24. On average, how many carers are needed for the caring of a person with LD and will this change throughout their lifetime e.g. more or fewer as people reach adulthood?

XI. Other considerations

25. Population indicated for metreleptin include children, are there any additional considerations required?

NICE National Institute for Health and Care Excellence

Technical engagement response form

Metreleptin for treating lipodystrophy [ID861]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm, 9 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text:

'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Fleur Taylor
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Amryt Pharmaceuticals DAC
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Questions for engagement

Issue 1: The clinical use of metreleptin in consideration of its current marketing authorisation/ Population that would be eligible for treatment	
1. Which patients with lipodystrophy would be eligible for metreleptin in clinical practice and what criteria would be used when it comes to the eligibility criteria?	In clinical practice, it is expected that, in line with the marketing authorisation, eligible lipodystrophy patients are defined as: - confirmed congenital generalised lipodystrophy or acquired generalised lipodystrophy in adults and children 2 years of age and above.(1) - 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.(1) Amryt recommends that in clinical practice further specific criteria are considered with the licence for patients with partial lipodystrophy based on baseline haemoglobin A1c (HbA1c) and triglyceride levels, defined as HbA1c>7.5% and/or fasting triglycerides >5.0 mmol/L. This has been developed based on the clinical evidence from the NIH studies 991265/20010769 and based on UK clinical expert experience. The HbA1c criteria could be lower under exceptional circumstances, such as extreme hyperphagia and/or

	severe side effects from other glucose lowering medications, or other serious complications of inadequate metabolic control such as progressive liver disease. Use of leptin levels are not recommended as a component of the eligibility criteria as they are not the basis of treatment goals, and only provide a general indication of a relative deficiency state that cannot be precisely predicted by a single threshold across individuals. Furthermore, severity of baseline metabolic status, as reflected by diabetes and/or hypertriglyceridemia, is a good predictor of response to metreleptin therapy.(2) Further to the eligibility criteria, Amryt have proposed a stopping rule for partial lipodystrophy patients and this is defined as: - At 9 months after metreleptin initiation, a specialist service review will determine whether treatment should be stopped if the following metabolic criteria have not been met: an HbA1c reduction of at least 0.75% from baseline, or a fasting triglyceride reduction of at least 50% from baseline.
2. The MA for the use of metreleptin in patients with partial lipodystrophy (PL) is not restrictive. Would you limit its use to a subgroup of patients and if so why? To your knowledge is there any consensus amongst UK experts treating patients with lipodystrophy in this?	As described in the response to Question 1, we would recommend the use of metreleptin in partial lipodystrophy (PL) is restricted to patients with 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,(1) defined as HbA1c>7.5% and/or fasting triglycerides >5.0

	mmol/L – clinically comparable to the PL subgroup in NIH studies 991265/20010769. The HbA1c criteria could be lower under exceptional circumstances, as described in response to question 1 above. In NIH studies 991265/20010769, a clinically meaningful and highly significant decrease in HbA1c and triglyceride level at Month 12 was demonstrated through the co-primary endpoints in the PL subgroup, more pronounced than in PL overall.(2)
3. Would you expect that the subgroup of people with PL (defined as HbA1c ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L) would have a different natural history from the overall PL population? Would you expect that the disease defined by the above characteristics would respond differently to metreleptin? Do patients with lower concentrations of leptin follow a different course and would you expect their response to metreleptin to differ from that of the full PL population?	It is expected that the partial lipodystrophy (PL) subgroup (defined as haemoglobin A1c (HbA1c) ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L) (2) would have a different natural history and response to metreleptin from the overall PL population because they have more severe metabolic disease. As such, they are at greater risk of developing complications associated with lipodystrophy. While leptin levels were used as part of the eligibility criteria for National Institutes of Health (NIH) studies 991265/20010769, they are not recommended for use in clinical practice. There is a large heterogeneity in leptin levels among lipodystrophy patients and leptin levels are not an appropriate marker to predict natural history of the disease nor response to metreleptin (see response to question 1). Metreleptin acts as exogenous leptin, supplementing endogenous leptin, and does not directly treat the lack or dysfunction of adipose cells that leads to low levels of leptin but substitutes for (in GL) or supplements (in PL) the endogenous leptin.

Issue 2: Representativeness of studies used to inform clinical effectiveness of metreleptin	
4. Are the populations in the main studies (the NIH study and the GL/PL natural history study) which were used to inform the indirect treatment comparison representative of those seen in UK clinical practice?	Amryt has established that the National Institutes of Health (NIH) studies are generalisable to United Kingdom (UK) clinical practice by consultation with UK clinical experts. Furthermore, as part of the earlier stages of this appraisal, it was concluded at the Final Evaluation Decision (FED) stage (FED now withdrawn) that, regarding NIH 991265/20010769 study, the NIH follow-up and FHA101, "only 1 patient in these studies was recruited from the UK, but the clinical experts confirmed that the trial populations were generalisable to patients seen in clinical practice in England."(3) As such, the largest and most comprehensive study for metreleptin was used in the indirect treatment comparison (ITC) analysis utilising the NIH follow-up study (metreleptin) with largest comparator study, the GL/PL Natural History Study (supportive care alone). There are differences in the baseline characteristics between the NIH follow-up study and GL/PL Natural History Study, with the GL/PL Natural History Study representing a less severe lipodystrophy population than for NIH studies 991265/20010769. The method employed for the ITC (inverse probability weighting) adjusted for potential confounders through covariates was selected in collaboration with clinical experts at Addenbrooke's (age, gender and lipodystrophy type). Results of the ITC demonstrated statistically significant and clinically meaningful benefits associated with metreleptin treatment as reflected by favourable changes in haemoglobin A1c (HbA1c), triglycerides, liver transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), and incidence of pancreatitis.
5. What is causing the discrepancy in the effects of metreleptin treatment noted (particularly with respect to	The figures used in this question do not align with the ERG report post-factual inaccuracy check and should be updated with the corrections provided by the company: ""For example, for GL patients there

changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a 12 months change in triglyceride levels from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke's EAP) vs. -10.54 mmol/l (NIH follow-up). Which treatment effect is more likely to be observed in future UK clinical practice?	was a 12 months change from 6.4 to ~~4.1 (about -2.3) mmol/l~~ 4.6 mmol/l and in patients with both baseline and Month 12 data the reduction was -3.5 mmol/l (Addenbrooke's EAP)" The observed treatment effect of metreleptin on change in absolute level of triglyceride level from baseline to Month 12 is related to the baseline level. As such, it is also important to consider percentage reductions at Month 12 compared to baseline. With regards to Month 12 change from baseline in triglyceride levels, mean percent change demonstrated greater consistency than the absolute change. For example, for GL patients the Month 12 percent change from baseline in triglyceride levels was Mean (SD) -48.4% (20.30) (Addenbrooke's EAP) vs. -32.1% (71.28) (NIH studies 991265/20010769).(2,4,5) The treatment effect likely to be observed in clinical practice is that of the indirect treatment comparison (ITC), which controls for covariates selected in collaboration with clinical experts at Addenbrooke's and compares the NIH follow-up (the most clinically relevant population to UK clinical practice) to the GL/PL Natural History study.
6. Would different criteria be used in the future for patients when it comes to metreleptin treatment than those required for in the EAP and would a different response be expected? If yes, in what way?	The EAP at Addenbrooke's began over a decade ago, and the patients eligible for the EAP have changed along with the growing evidence base for lipodystrophy patients. As such, clinicians have allowed less severe lipodystrophy patients in the EAP in the past than they would today, during the time in which clinical understanding of lipodystrophy was rapidly evolving. Following a NICE recommendation for the use of metreleptin, the more severe partial lipodystrophy (PL) patients aligned to the PL subgroup in the National Institutes of Health (NIH) 991265/20010769 studies would be initiated on treatment with metreleptin alongside a proposed stopping rule (see response to question 1). Addenbrooke's are preparing for enhanced data collection of patients on metreleptin

	following a NICE recommendation and this will provide further insights to monitor the real-world response to metreleptin in lipodystrophy patients in England.
Issue 3: The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison	
7. Limited number of covariates were adjusted for in the ITC conducted by the company, are those covariates (namely, age, gender and lipodystrophy type) the most important and relevant for baseline difference adjustment to predict the course of the disease? Would stakeholders expect to see the absolute change in HbA1c and triglyceride levels associated with metreleptin treatment vary with baseline HbA1c or triglyceride level?	The covariates (age, gender and lipodystrophy type) were selected in collaboration with clinical experts at Addenbrooke's to ensure the most appropriate covariates for affecting both treatment assignment and the outcomes of interest were chosen. Lipodystrophy type and age were identified by United Kingdom (UK) clinical experts as the most significant predictors of disease progression. Absolute changes in haemoglobin A1c (HbA1c) and triglyceride levels associated with metreleptin treatment are dependent on baseline HbA1c or triglyceride levels. Baseline HbA1c and triglyceride levels are dependent on age and reflective of stage of the disease. A sensitivity analysis considering these additional covariates was explored. However, the analysis was not feasible. When increasing the number of covariates in the ITC, this increases the number of dimensions on which individuals must have been similar in order to match propensity scores, in turn reducing the pool of comparable individuals between the two study populations.(6) Inclusion of excess covariates thereby increased the variance of the results and caused an avoidable loss of precision.

8. Would it be appropriate to use the EAP (Early Access Programme) study, which includes only UK patients at Addenbrooke's Hospital, instead of the NIH study for the ITC?

Table 1 provides a comparison of baseline characteristics between the Addenbrooke's Early Access Programme (EAP) and NIH studies 991264/200110769 (105 patients identical to the NIH follow-up study).

Gender and proportion of adult lipodystrophy patients (≥18 years) appear comparable across the Addenbrooke's EAP and NIH studies 991264/200110769. Some differences exist in proportion of patients with elevated haemoglobin A1c (HbA1c) and elevated triglyceride levels, most notably in the PL populations where patients appear less severely affected in the Addenbrooke's EAP in comparison to NIH studies 991264/200110769.

As noted in response to question 6, less severe lipodystrophy patients were included in the EAP in the past than would be expected in the future. Therefore, it would be expected that treatment response to metreleptin would be comparable between future UK lipodystrophy patients on metreleptin and NIH studies 991264/200110769/the NIH follow-up study.

Table 1: A comparison of baseline characteristics between the Addenbrooke's EAP and NIH studies 991264/200110769 (105 patients identical to the NIH follow-up study)

Characteristic	Addenbrooke's EAP (N=31)			NIH studies 991265/200110769 (N=107)		
	GL (N = 10)	PL (N = 21)		GL (N = 66)	PL (N = 41)	
		PL subgroup[a] (N = 18)	Overall (N = 21)		PL subgroup[a] (N = 31)	Overall (N = 41)
Female, n (%)	7 (70.0)	16 (88.9)	19 (90.5)	51 (77.3)	30 (96.8)	40 (97.6)
Age, median (range)[b]	1 (1, 21)	23 (1, 53)	34.5 (1, 53)	15.0 (1.0, 68.0)	38.0 (15.0, 64.0)	34.0 (10.0, 64.0)
<18 years, n(%)	5 (71.4)	2 (28.6)	2 (20.0)	45 (68.2)	5 (16.1)	8 (19.5)
≥18 years, n(%)	2 (28.6)	5 (71.4)	8 (80.0)	21 (31.8)	26 (83.9)	33 (80.5)

HbA1c, %[b]						
Median (range)	9.1 (5.1, 13.5)	7.3 (6.2, 15.3)	7.1 (5.7, 15.3)	8.7 (4.5, 13.7)	8.6 (5.7, 13.3)	7.8 (4.6, 13.3)
≥6.5, n (%)	8 (88.9)	16 (88.9)	17 (81.0)	49 (74.2)	29 (93.5)	29 (70.7)
≥8.0, n (%)	8 (88.9)	7 (38.9)	7 (33.3)	42 (63.6)	19 (61.3)	19 (46.3)
Fasting triglycerides, mmol/L[b]						
Median (range)	4.6 (1.7, 17.1)	3.4 (1.5, 26.5)	3.2 (1.1, 26.5)	4.6 (0.6, 143.3)	5.5 (1.2, 109.5)	4.1 (1.1, 109.5)
≥2.26 mmol/L, n(%)	9 (90.0)	14 (82.4)	15 (75.0)	50 (75.8)	27 (87.1)	34 (82.9)
≥5.65 mmol/L, n(%)	5 (50.0)	2 (11.8)	2 (10.0)	26 (39.4)	15 (48.4)	15 (36.6)

Abbreviations: GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; PL, Partial lipodystrophy.

[a]PL subgroup, patients with HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L. Leptin cut-offs were also defined as part the study inclusion criteria for NIH studies 991265/200110769 and as baseline leptin <12 ng/mL for the Addenbrooke's EAP.

[b]Where data are available. Age of diagnosis is available for Addenbrooke's EAP and age of metreleptin initiation for NIH studies 991265/200110769.

Source: Combined data on file (4,5) and NIH studies 991265/20010769 CSR (2)

The NIH follow-up study is the most comprehensive and largest dataset available on metreleptin treatment and has been validated by UK clinical experts as generalisable to UK clinical practice. As such, the NIH follow-up study has been employed in the ITC analyses to provide robust clinical effectiveness estimates, demonstrating statistically significant and clinical meaningful reductions in HbA1c and triglycerides for patients treated with metreleptin compared to supportive care.

Whilst the EAP does represent a sample of patients treated in the UK, as noted in response to question 6, there have been changes in the understanding of lipodystrophy over the course of this programme that

was initiated over a decade ago, and therefore does not wholly represent the patient metabolic profile that will be initiated on metreleptin in the future following a positive NICE recommendation.

Furthermore, limitations associated with the much smaller sample size of the EAP dataset (N=31) compared to the NIH follow-up study (N=105) are important to consider (Table 2). The sample size for the EAP is further compounded by the availability of complete data at the follow-up timepoint and at baseline. For both Month 12 change from baseline in HbA1c and Month 12 change from baseline in triglyceride levels, 101 lipodystrophy patients had complete data in the NIH follow-up, in comparison to only 12 lipodystrophy patients in the Addenbrooke's EAP. Consequently, it is not feasible to run a meaningful ITC based on the sample size available in the Addenbrooke's EAP dataset.

Table 2: Data available for relevant outcomes - comparison of Addenbrooke's EAP vs. NIH follow-up study

Data available for Month 12 change from baseline	Addenbrooke's EAP (N=31)	NIH follow-up study (N=105)
HbA1c, n(%)	12 (38.7)	101 (96.2)
Triglyceride, n(%)	12 (38.7)	101 (96.2)
ALT, n(%)	NR	99 (94.3)
AST, n(%)	NR	99 (94.3)
Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GL, Generalised lipodystrophy; HbA1c, Haemoglobin A1c; NR, Not recorded; PL, Partial lipodystrophy		

Source: Combined data on file (4,5)

Issue 4: Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD

9. What is the stakeholder's view on the long term treatment effect of metreleptin on clinical outcomes such as organ abnormalities (liver, kidney and heart) and female reproductive dysfunction? Is there any reason that these abnormalities and dysfunction would not continue to occur at a rate consistent with future levels of HbA1c and triglycerides while patients are having metreleptin treatment in the longer term?	The Delphi panel reached consensus that haemoglobin A1c (HbA1c) is a good predictor of diabetes-related complications covering cardiovascular disease, kidney, retinopathy and neuropathy outcomes in lipodystrophy patients.(7) The relationship of HbA1c with long-term hard outcomes is established and widely accepted based on a wide range of studies including the 30-year follow-up of diabetes in the Diabetes Control and Complications Trial (DCCT) / Epidemiology of Diabetes Interventions and Complications (EDIC) and the 30-year follow-up of diabetes United Kingdom Prospective Diabetes Study (UKPDS) study.(8–13) Therefore, employing the surrogate outcome of HbA1c to predict long term outcomes is appropriate. As such, in the cost-effectiveness model, the company assumed that abnormalities and dysfunction would continue to occur at a rate consistent with future levels of HbA1c and triglycerides while patients are having metreleptin treatment in the longer term.
10. What is the stakeholder's view on the long term treatment effect of metreleptin on patient reported outcomes such as hyperphagia and quality of life?	The long-term quality life benefits for patients on metreleptin compared to standard of care are driven by improved management of the disease resulting from the reduction in lipodystrophy symptoms, such as hyperphagia, and risk of future complications. The long-term benefits of metreleptin therapy have been demonstrated in studies via haemoglobin A1c (HbA1c) and triglycerides, which are robust predictors of complications.(7) The long-term results of the primary endpoint in National Institutes of Health (NIH) 991265/20010769 studies up to 48 months in generalised lipodystrophy and 36 months in the partial lipodystrophy subgroup showed sustained clinically meaningful improvements in key measures of disease status (HbA1c and

	triglyceride levels) (shown in figure 15 of the company submission).(14) Complementary evidence from Addenbrooke's Hospital Early Access Programme provides support for this, with sustained improvements in glycaemic control and hypertriglyceridaemia in both generalised lipodystrophy and partial lipodystrophy subgroup patients observed up to 36 months (further detailed in Section 9.6 of company submission).(15)
11. There are case reports of neutralizing antibody limiting the effect of metreleptin. Would stakeholders expect that to be the case in a significant proportion of treated patients and what impact would be expected on outcomes such as HbA1c and triglycerides in the long term?	The company does not expect that neutralising antibodies will affect a significant proportion of patients or affect outcomes such as haemoglobin A1c (HbA1c) and triglycerides in the long-term. In order to support the proposed product information for the marketing authorisation application to the European Medicines Agency, safety data were pooled across studies and lipodystrophy type. Neutralising were antibodies were reported in 4% of patients.(2,16) If there is evidence of diminishing efficacy of metreleptin, then clinicians are encouraged to request an assay for presence of neutralising antibodies. Ultimately the decision regarding continued treatment is based on an individual benefit-risk assessment, taking into account several factors including patients' metabolic status and symptoms.
12. For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume? If yes, by what mechanism? If this is thought likely, for how long a continued effect	Metreleptin acts centrally to decrease plasma glucose, triglycerides and other lipid intermediates, reducing their ectopic accumulation in tissues and organs, and ameliorating severe insulin resistance and organ damage. While patients receive metreleptin therapy, they will benefit from an improvement in the associated insulin resistance, improved glycaemic control and a slowing in the progression of multi-organ damage. Patients remain on metreleptin therapy for several years before discontinuation and this provides sufficient time for benefits to accrue, particularly slowing of glycaemic-related tissue damage and

of metreleptin treatment on the above outcomes is clinically plausible? And how much?	accumulation of ectopic fat in the liver. In the Evidence Review Group's (ERG) preferred base-case model, the average time to treatment discontinuation is estimated as 8.61 years. These benefits manifest through a reduction of symptoms and a reduction in the risk multiple complications (such as cardiovascular disease or liver disease), in turn generating quality of life benefits to both patients and carers compared to those patients on standard of care. To explore the uncertainty around the post-discontinuation assumptions, the company has run scenarios exploring the return of haemoglobin A1c (HbA1c) to pre-treatment baseline levels upon treatment discontinuation, as well as scenarios exploring the continuation of quality of life (QoL) treatment benefit (patient and carer) and liver treatment benefit for distinct time periods post-discontinuation. Full details of the analyses are presented below. All analyses were run using the company's updated base case assumptions (as per the response to questions 15 and 24) with a cohort of 3,000 patients using a fixed seed of random numbers. Where applicable, the incremental cost-effectiveness ratios (ICERs) have been adjusted according to the NICE HST process guide (17) to reflect the significant QALY gains (>10 incremental undiscounted QALYs) for treated patients. The ERG amended the ICER calculation in the model, however, this did not account for the ICER adjustment in instances where >10 undiscounted QALYs have been achieved. As such, the company has updated the model to adjust the ICERs (QALY weighting applied) for scenarios in which treated patient accrue >10 undiscounted QALYs. <u>HbA1c</u>

	Partial lipodystrophy is associated with severe insulin resistance in some patients. This results in sustained elevation in plasma glucose reflected over time by increased glycosylation of haemoglobin (HbA1c). Elevated levels of HbA1c are used as measure of glucose control over time and reflect levels over several months. Control of elevated blood glucose is a goal of treatment to avoid the complications of diabetes caused either directly or indirectly by elevated blood glucose levels, such as cardiovascular disease, retinopathy, nephropathy and peripheral neuropathy. These diabetic complications develop over many years at a rate and extent that is related to the adequacy of glucose control. It would be expected therefore, that the benefit of controlling blood glucose with metreleptin, would decline at a rate that is similar to that which applies to the accumulation of benefit with continued treatment. It would be clinically implausible to assume that the rate of loss of benefit in the avoidance of complications would be instant, and revert to standard of care rates (including a 0.15% annual drift) following metreleptin discontinuation. To minimise the uncertainty related to the level of residual benefits that are maintained after metreleptin discontinuation, alternative scenario analyses have been explored, whereby upon treatment discontinuation, HbA1c marker level returns to baseline (not including a 0.15% annual drift) at the point of discontinuation (rather than above the baseline level as implemented by the ERG's amendment). This assumes the same trajectory for patients on standard of care treatment at the start of the model. To remain conservative, in instances where the reversal of HbA1c to baseline level results in a lower HbA1c than the HbA1c level prior to discontinuation (as a result of the 0.15% annual drift), the highest HbA1c value applies. Due to the modelling accounting for patients' HbA1c levels plateauing at 12%

through the annual drift rate of 0.15%, the eventual paths of the standard of care patients and those discontinuing on metreleptin merge.

The company's updated base-case has been re-run with this scenario included, with results presented in Table 3 below. This compares to the company's updated base-case ICER of £118,895 per QALY for the overall population (see response to question 24), where HbA1c benefits are maintained post-discontinuation.

Table 3: Reversion of HbA1c to baseline upon discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	91,407
PL metreleptin	[redacted]	[redacted]	161,875
Metreleptin overall	[redacted]	[redacted]	119,997

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; *QALY weighting applied

Liver

UK clinicians agree that residual liver benefits will be maintained post-discontinuation under the assumption that a reduction in fatty deposits and accumulation in the liver achieved while on metreleptin treatment will yield a longer-term benefit and slow the progression of the disease.

In a patient discontinuing metreleptin therapy, it is not clinically plausible that the physical level of liver damage would instantly reverse to be that of a patient in the standard of care arm if they have received

	several years of metreleptin therapy. It is incorrect to consider the presence of fat in the liver as a direct measure of harm. Triglyceride accumulation leads to inflammation (non-alcoholic steatohepatitis or NASH) that may then lead to fibrosis (scarring). The presence of fibrotic liver disease then increases the risk of progression to cirrhosis. Therefore, a reduction of hepatic fat content over several years would be expected to cause a cumulative benefit related to a reduced inflammatory stimulus and decreased risk of progressive disease. Withdrawal of metreleptin treatment would certainly be expected to result in an increase in hepatic fat associated with ectopic deposition as systemic triglyceride levels rise over several weeks. However, it would take several years to return to a baseline level of risk for progressive liver disease as the underlying causative pathology evolves slowly over time. However, the ERG's base-case assumptions assume this by removing all liver benefits immediately following metreleptin discontinuation. The company has also explored scenarios to address the uncertainty regarding the longer-term reduction in the risk of liver complications for patients after they discontinue metreleptin. As stated above, based on the Evidence Review Group's (ERG) preferred base-case, the average time to discontinuation is estimated as 8.61 years. The treatment benefits for the liver sub-model have now been modelled for 1-year post-discontinuation, 5 years post-discontinuation and 9 years post-discontinuation (average time to treatment discontinuation rounded to account for the annual cycle length). The company's updated base-case (further detailed in the response to question 24 below) has been re-run with these scenarios, resulting in the incremental cost-effectiveness ratios (ICERs) displayed below.

This compares to the company's updated base-case ICER of £118,895 per QALY for the overall population (see response to question 24).

Table 4: Maintenance of liver benefits for 1-year post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	116,642.13
PL metreleptin	[redacted]	[redacted]	162,804.41
Metreleptin overall	[redacted]	[redacted]	138,087

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; * QALY weighting applied

Table 5: Maintenance of liver benefits for 5 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	108,790
PL metreleptin	[redacted]	[redacted]	161,283
Metreleptin overall	[redacted]	[redacted]	132,380

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; * QALY weighting applied

Table 6: Maintenance of liver benefits for 9 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	103,704
PL metreleptin	[redacted]	[redacted]	160,152

Metreleptin overall	[redacted]	[redacted]	128,492	

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; *QALY weighting applied

Quality of life

UK clinicians agree that it is clinically implausible to assume that treatment benefits associated with metreleptin would be reversed immediately upon discontinuation, as per the ERG's preferred base-case, and that a patient would return to the same disease trajectory as a supportive care-treated patient.

Some symptoms, such as hyperphagia, or markers, such as HbA1c, will return in a short period. However, given that lipodystrophy is a chronic progressive disease, the company believes it is reasonable to assume that a patient treated with metreleptin post-discontinuation will have slower glycaemic-related tissue damage and accumulation of ectopic fat in the liver compared to a patient who has never been treated with metreleptin, and will therefore maintain residual quality of life benefit post-discontinuation until death. This in turn will translate to a similar quality of life benefit for patients' carers.

To minimise the uncertainty around the residual level of quality of life benefits for patients and carers after metreleptin discontinuation, the company has also explored a further 3 scenarios applied to the company's updated base-case. The scenarios comprise patients retaining 50% of the differential utility benefit and carer utility benefit for: 1-year post discontinuation, 5 years post-discontinuation and 9 years post-discontinuation (assumed average time to treatment discontinuation). Based on the ERG's preferred base-case, the average time to discontinuation is 8.61 years. The treatment benefits have been modelled for 9 years post-discontinuation for the latter scenario to align with the annual cycle length. The

company's updated base-case (further detailed in the response to question 24 below) has been re-run with these scenarios, resulting in the incremental cost-effectiveness ratios (ICERs) displayed below. This compares to the company's updated base-case ICER of £118,895 per QALY for the overall population (see response to question 24).

Table 7: Maintenance of 50% QoL treatment and carer benefits for 1-year post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	148,869
PL metreleptin	[redacted]	[redacted]	219,267
Metreleptin overall	[redacted]	[redacted]	180,575

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Table 8: Maintenance of 50% QoL treatment and carer benefits for 5 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	140,269
PL metreleptin	[redacted]	[redacted]	199,738
Metreleptin overall	[redacted]	[redacted]	167,551

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Table 9: Maintenance of 50% QoL treatment and carer benefits for 9 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	133,402
PL metreleptin	[redacted]	[redacted]	185,869
Metreleptin overall	[redacted]	[redacted]	157,755

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Cumulative scenarios

The cumulative results of the scenarios above, for residual post-discontinuation benefits maintained for: 1 year, 5 years and 9 years (all alongside reversion of HbA1c level to baseline upon discontinuation) have also been run, with results presented below:

Table 10: Residual post-discontinuation benefits maintained for 1-year post-discontinuation and reversion of HbA1c to baseline

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	162,611
PL metreleptin	[redacted]	[redacted]	231,396
Metreleptin overall	[redacted]	[redacted]	194,263

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Table 11: Residual post-discontinuation benefits maintained for 5 years post-discontinuation and reversion of HbA1c to baseline

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	148,224
PL metreleptin	[redacted]	[redacted]	207,973
Metreleptin overall	[redacted]	[redacted]	175,917

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Table 12: Residual post-discontinuation benefits maintained for 9 years post-discontinuation and reversion of HbA1c to baseline

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	138,117
PL metreleptin	[redacted]	[redacted]	191,811
Metreleptin overall	[redacted]	[redacted]	163,130

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

For ease of interpretation a summary of the results from all scenarios are presented below:

Table 13: Summary of scenario analyses

Scenario	ICER (non-cumulative unless stated otherwise)		
	Benefits maintained for 1 year post-discontinuation	**Benefits maintained for 5 years post-discontinuation**	**Benefits maintained for 9 years post-discontinuation**
Liver benefits	£138,087	£132,380	£128,492
Treatment differential utility benefit and carer benefit (both at 50%)	£180,575	£167,551	£157,755
HbA1c reversion to baseline upon discontinuation	£119,997 (length of time post discontinuation benefits maintained not applicable in this scenario)		
Cumulative ICER	£194,263	£175,917	£163,130

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

13. Is there a correlation between surrogate outcomes such as HbA1c and clinical outcomes such as cardiovascular and kidney diseases in people with LD and is this the same	A Delphi Panel (which included UK clinical experts) reached consensus on the correlation between surrogate outcomes such as haemoglobin A1c (HbA1c) and triglycerides, and clinical outcomes in

as seen in other diseases, for example, diabetes?	patients with lipodystrophy.(7) Specifically, to determine whether the cause of key organ specific complications in lipodystrophy are attributable to: • Elevated triglycerides • Elevated HbA1c • Other diabetes-related cause (outside of the effect of elevated triglycerides/HbA1c) • Other lipodystrophy-related cause (outside of the effect of elevated triglycerides/HbA1c and other diabetes-related causes) • Two or more of the above independently • None of the above. Consensus was achieved amongst the Delphi Panel clinical experts that HbA1c is a predictive factor in the development of kidney disease, retinopathy, neuropathy, and cardiovascular disease in lipodystrophy patients. Please note that we acknowledge HbA1c directly does not cause organ-related damage and that, more accurately, HbA1c is a strong biochemical surrogate for the sustained elevation of plasma glucose, which is a key contributor to the development of diabetes-related organ damage in lipodystrophy. The relationship between the glycaemic control marker HbA1c and the risk of diabetes-related complications has been established by a wide range of studies in diabetes patients, including the 30-year follow-up of diabetes in the Diabetes Control and Complications Trial (DCCT) / Epidemiology of Diabetes

	Interventions and Complications (EDIC) and the 30-year follow-up of diabetes United Kingdom Prospective Diabetes Study (UKPDS) study.(8–13) It has been established that a reduction in HbA1c reduces the risk of diabetes-related complications over the long-term and mortality. Given the common observed insulin resistance observed in lipodystrophy patients and diabetes patients, it can be assumed that the relationships observed between HbA1c and clinical outcomes from other diseases – in particular early-onset type 2 diabetes – are relevant and applicable to patients with lipodystrophy. Clinical expert opinion has highlighted that the insulin resistance in lipodystrophy is more severe than in diabetes and is likely to lead to worse organ-related damage, independent of glucose levels. Therefore, whilst HbA1c serves as a suitable surrogate for clinical outcomes in lipodystrophy, the transition probabilities in the model are likely to be conservative. In the company's base-case, no further surrogates were employed to predict hard clinical outcomes.
Issue 5: Discontinuation rate of metreleptin treatment	
14. What discontinuation rate on metreleptin treatment is likely to be seen in UK clinical practice?	The company used the rate of annual discontinuation based on treatment non-compliance from National Institutes of Health (NIH) studies 991265/200110769 to represent the discontinuation rate likely to be seen in UK clinical practice.(14) Discontinuations due to all reasons observed in the NIH studies 991265/200110769 also accounted for patients that discontinued the studies prematurely to enter the Early Access Programme for metreleptin initiated in the US prior to FDA approval.

15. Is a constant annual discontinuation rate of 1.50% for GL patients and 3.86% for PL patients from NIH study representative of what would happen in clinical practice? Alternatively is a declining rate of 8.93% in year 1 (which closely reflects the discontinuation observed in the first year of the NIH trial), and 5.63% in years 2-9 and 2.04% in years 10 onwards (representing the decline in discontinuation over time)more plausible?	The company accepts that the declining rate of discontinuation presented are plausible alternative discontinuation rates that have been previously accepted by the NICE Committee at the Final Evaluation Document (FED) stage and the company's base case has now been updated with these discontinuation rates. Please refer to Table 23 for the updated company base-case ICER results.
Issue 6: Baseline transition probabilities and pathway through organ sub-models	
16. Is it appropriate to assume that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but caused by different underlying diseases, and therefore patients with lipodystrophy will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions but caused by different underlying disease states?	As explained in the company submission section 12.2.1, the Delphi Panel which included UK clinicians reached consensus that early-onset type 2 diabetes as the closest form of diabetes observed in lipodystrophy patients. To reflect this, baseline transition probabilities in the model were adjusted using risk ratios, which were converted from odds ratios, where appropriate for organ-specific complications derived from literature for type 1 versus early-onset type 2 diabetes. Therefore, based on the available evidence, the transition probabilities in the model closely reflect the disease trajectory of lipodystrophy patients.

	Furthermore, triglycerides are not used in the cost-effectiveness model to derive or adjust transition probabilities. As such, the risk of complications is expected to be underestimated for complications such as cardiovascular disease.
17. Can the stakeholders provide feedback on the extent to which these input values and transition probability estimates are generalisable to patients with lipodystrophy? Are the populations used to estimate transition probabilities generalisable for UK clinical practice?	Given that the Delphi Panel (which included UK clinical experts) reached consensus on the appropriateness of using haemoglobin A1c (HbA1c) levels to inform the rate of disease progression for the kidney, retinopathy, neuropathy and cardiovascular sub-models; and the relative-risk adjustment applied to transition probabilities (as outlined in response to question 16 above), the company has assumed that the transition probability estimates are generalisable to patients with lipodystrophy in the UK. The Sheffield Diabetes model, used to inform the transition probabilities for the sub-models listed above, was predominantly populated using data from patients in the UK and used in previously NICE-accepted cost-effectiveness analyses of a UK population – and therefore are generalisable to UK clinical practice. With regard to the liver sub-model, the decision to obtain transition probabilities from the NICE non-alcoholic fatty liver disease (NAFLD) guideline (18), was based on clinical experts highlighting that the liver disease complications observed in lipodystrophy patients are analogous to that associated with non-alcoholic fatty liver disease. As such, the company believe that the transition probabilities employed in the liver sub-model are also generalisable to patients with lipodystrophy and generalisable for UK clinical practice.

18. Is it appropriate to use HbA1c or ALT/AST to adjust the transition probabilities and account for the reduction in risk of organ complications associated with metreleptin in sub-models?	For the reasons outlined in the response to question 13, we have ascertained that HbA1c level and glycaemic-related tissue damage are a key driver of organ complications in patients with lipodystrophy. Therefore, the use of HbA1c to adjust transition probabilities and account for the reduction in risk of organ complications associated with metreleptin is justified. Please see responses to question 13 and 19 for further details. UK expert opinion was sought in the model development stage concerning the suitability using surrogate markers of liver outcomes. With respect to alanine transaminase (ALT) and aspartate aminotransferase (AST), clinicians advised that these are poor predictors of liver outcomes. A preferred measure for predicting liver outcomes is fibrosis 4 (Fib-4) score. However, there is insufficient data on platelet levels (one of key components of Fib-4) to allow the use Fib-4 score in the indirect treatment comparison or cost-effectiveness model. As such, the Delphi Panel (7) was used to elicit direct estimates for the risk reduction of liver outcomes as a result of metreleptin treatment compared with standard of care for lipodystrophy patients and this was utilised in the company's base-case analysis.
Issue 7: Metreleptin's continued treatment effect on HbA1c post-discontinuation	
19. (1st part of question 19) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?	Please see the response to question 12 with respect to the clinical rationale for the continuation of benefits in the longer term after discontinuation. In the cost-effectiveness model, haemoglobin A1c (HbA1c) is used as proxy to determine the risk of diabetes-related complications in lipodystrophy, as reflected in the transition probabilities. In clinical practice, however, HbA1c is used as a current marker of glycaemic control and we agree that following discontinuation of metreleptin, the HbA1c marker will go up within a few months. However, glycaemic-

related tissue damage (the driver of diabetes-related complications in lipodystrophy) will not revert in the same manner as the HbA1c marker in a patient after metreleptin is discontinued. It is this latter point that is most pertinent with respect to how the benefits accrued while on metreleptin treatment, will materialise into longer-term reductions in the risk of complications and the options for how to capture these from a modelling perspective. In the company's submission, the mechanism in which longer-term reduction in the risk of complications was captured from a modelling perspective was by maintaining HbA1c levels and liver benefits for a lifetime after patients discontinue metreleptin.

The average time to treatment discontinuation based on the ERG model amendments, is 8.61 years. This is a substantial time period for treatment-related benefits to accrue and reduce the risk of diabetes-related complications via the slowing down of glycaemic-related tissue damage. As such, the company maintains that the ERG's base-case analysis is unrealistic where the HbA1c marker jumps to the same as a standard of care patient that has never received metreleptin treatment and reflects no residual, longer-term reductions in glycaemic-related tissue damage (risk of diabetes-related complications) from that point onwards.

The company ran a scenario analysis to explore a scenario where the HbA1c level reverts to the baseline level upon treatment discontinuation, with results presented below in Table 14. Please see the response to question 12 for the full details of the scenario analysis.

Table 14: Reversion of HbA1c to baseline upon discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	91,407

	PL metreleptin | [redacted] | [redacted] | 161,875 **Metreleptin overall** | [redacted] | [redacted] | 119,997 ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; *QALY weighting applied
20. Is it appropriate to assume that, post-discontinuation of metreleptin treatment, the relative efficacy of metreleptin compared with supportive care would remain constant over the life time, and the change in HbA1c level will be the same in the metreleptin and supportive care groups?	As outlined in the response to question 12, the relative efficacy post-discontinuation compared to supportive care treatment only remains until the ceiling value of 12% HbA1c. After reaching this ceiling value, the HbA1c remains constant in both metreleptin-treated and supportive care-treated patients. The HbA1c annual increase of 0.15% applied to both treatment arms was obtained from NICE TA315, where a 0.15% annual HbA1c increase was applied to patients treated with insulin therapy.(19)
21. Would a scenario in which only a proportion of patients would experience the 0.15% increase in HbA1c after the 1st cycle be possible?	A lack of data currently exists to address this uncertainty, specifically pertaining to the proportion of patients within each arm that would be subject to a different rate of increase. The company has conducted scenario analyses exploring a scenario in which all patients experience a 0.1% annual HbA1c increase and a scenario in which all patients experience a 0.05% annual HbA1c increase. The results of the scenario analyses are presented below. This would suggest the updated base-case represents a conservative estimate of cost-effectiveness. **Table 15: All patients experience a 0.1% annual increase in HbA1c** **Population** | **Incremental costs (£)** | **Incremental QALYs** | **ICER (£)** **GL metreleptin** | [redacted] | [redacted] | 81,600 **PL metreleptin** | [redacted] | [redacted] | 155,392

Metreleptin overall	[redacted]	[redacted]	110,223	

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; *QALY weighting applied

Table 16: All patients experience a 0.05% annual increase in HbA1c

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	71,831
PL metreleptin	[redacted]	[redacted]	153,529
Metreleptin overall	[redacted]	[redacted]	101,368

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; *QALY weighting applied

Issue 8: Metreleptin's continued treatment effect on liver complications post discontinuation

19. (2nd part of question 19) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?

This question is a duplication of question 19 under issue 7. Please see the response to question 19 under Issue 7 above.

If this question related to issue 8 about liver benefits, please see the response to question 12. As further detailed in question 12, scenario analyses exploring the maintenance of liver treatment benefits for 1 year, 5 years and 9 years post-discontinuation have been undertaken, with results presented below:

Table 17: Maintenance of liver benefits for 1-year post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	116,642

PL metreleptin	[redacted]	[redacted]	162,804
Metreleptin overall	[redacted]	[redacted]	138,087

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; * QALY weighting applied

Table 18: Maintenance of liver benefits for 5 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	108,790
PL metreleptin	[redacted]	[redacted]	161,283
Metreleptin overall	[redacted]	[redacted]	132,380

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; * QALY weighting applied

Table 19: Maintenance of liver benefits for 9 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	103,704
PL metreleptin	[redacted]	[redacted]	160,152
Metreleptin overall	[redacted]	[redacted]	128,492

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; *QALY weighting applied

Issue 9: Metreleptin's continued treatment effect on quality of life (utility differential) post-discontinuation and assumptions around additional utilities used in the model

22. Is it appropriate to use utility values from the literature based on populations with disorders other than LD, on which the sub-models are based and apply them to LD populations at the same state in the model?	Given the ultra-orphan nature of the condition, a lack of lipodystrophy-specific utility values exists in the literature, as identified by the company's systematic literature review presented in section 10.1.6 of the company submission. As such utility values, where available, were selected based on their acceptance in previous NICE appraisals or their use in NICE guidelines. The company acknowledge that the overall utility of patients suffering from lipodystrophy will be different from the overall utility of patients with similar metabolic abnormalities but caused by different underlying diseases. However, the utility decrement of a specific symptom or complication as a result of a particular condition would not be significantly influenced by the aetiology of that condition. For example, the disutility experienced by a diabetes patient suffering from peripheral neuropathy is similar to that of a lipodystrophy patient suffering the same complication. As such, the health state utility values employed in the cost-effectiveness model are representative of those complications experienced by lipodystrophy patients.
23. Is it appropriate to assume additional differential in utility (measure of QoL) between patients receiving metreleptin and standard of care (0.12 based on the DCE study) to account for changes in quality of life not captured by the health states in the sub-models? Similarly should there be a disutility due to the burden of caring in the models? If yes, is it appropriate to assume that some of these additional utilities would be	Data from the National Institutes of Health (NIH) follow-up study (20), as further detailed in the response to question B11 in the company response to the Evidence review Group (ERG) clarification questions, demonstrates that metreleptin has been shown to improve several symptoms associated with lipodystrophy, that have not been captured through the six sub-models. These symptoms include: hyperphagia, impaired physical appearance, disruption to female reproductive functioning and inability to perform work/schoolwork. As such, an additional differential in utility between metreleptin-treated patients and supportive care-treated patients is essential to capture the above symptoms and elucidate the true utility benefit as a result of metreleptin treatment.

maintained post-discontinuation (over the patient's lifetime) and why?

Section 7.1.4 in the company submission outlines the significant impact of lipodystrophy on caregivers, as further supported by the *Lipodystrophy Caregiver Disease Burden Survey*. Based on this research, the company maintains that a disutility due to the burden of caring is justified in the economic model.

As answered in question 12, given that metreleptin slows the progression of the disease – and therefore reduces the risk of future complications, those patients who have previously been treated with metreleptin will maintain some residual quality of life benefit post-discontinuation compared to supportive-care treated patients. As explained in the response to question 12, the average time to treatment discontinuation is estimated as 8.61 years by the ERG's preferred base-case, during which time significant benefits will have accrued in terms of slowing of disease progression.

As further detailed in question 12, scenario analyses exploring the maintenance of 50% of the treatment differential utility benefit and 50% of the carer utility benefit maintained for 1 year, 5 years and 9 years post-discontinuation have been undertaken, with results presented below:

Table 20: Maintenance of 50% QoL treatment and carer benefits for 1-year post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	148,869
PL metreleptin	[redacted]	[redacted]	219,267
Metreleptin overall	[redacted]	[redacted]	180,575

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Table 21: Maintenance of 50% QoL treatment and carer benefits for 5 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	140,269.14
PL metreleptin	[redacted]	[redacted]	199,738.34
Metreleptin overall	[redacted]	[redacted]	167,551

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Table 22: Maintenance of 50% QoL treatment and carer benefits for 9 years post-discontinuation

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	133,402
PL metreleptin	[redacted]	[redacted]	185,869
Metreleptin overall	[redacted]	[redacted]	157,755

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

Issue 10: Number of carers used in the model

24. On average, how many carers are needed for the caring of a person with LD and will this change throughout their lifetime e.g. more or fewer as people reach adulthood?	Number of carers The company has applied two carers per patient. This is based on the median from the *Lipodystrophy Caregiver Disease Burden Survey.* Due to the ultra-orphan nature of the condition, and the potential impact of outliers having a large impact on the mean, the company believes that the median number of

	carers per patient from the caregiver survey, is more likely to be representative of the average number of carers in UK clinical practice. The number of carers per patient has been validated by UK patient experts. Use of UK Tariff consistently across utilities Based on discussion from the NICE technical engagement teleconference (held on 19th August 2020) and the Evidence Review's (ERG) response to Issue 2 in the factual inaccuracy check, the company agrees that there should be consistency across the tariffs used to calculate all utilities applied in the cost-effectiveness model. The company has identified that the baseline age-dependent utilities used the company and the ERG's base carer use the England-specific tariff, while the health state utilities and carer dis-utilities use the UK Tariff. As such, the company base-case and the ERG's preferred base-case, have been updated such that the baseline age-dependent utilities are also UK-specific values, which aligns with the health state utility values and carer disutility values in the model. This approach is consistent with NICE Decision Support Unit (DSU) recommendations in Technical Support Document (TSD) 8 (21) and previous approaches accepted for carer disutility valuations in NICE appraisals, for example HST9, TA473 and TA527 (22–24). The NICE DSU TSD 8 states: "It is recommended that the methods used to measure HRQL for the caregiver is the same as that used for the patients. This implies the use of the EQ-5D with the UK population tariff". There is no such recommendation to use the UK-England tariff. The updated base-cases have both been run with 1 cohort of 3,000 using a fixed seed of random numbers:

- Updated *company base-case ICER*, overall (discounted) (assumptions as per company submission [maintains the assumption of life time benefits], with updated baseline age-dependent utilities based on UK Tariff, updated ICER calculation as per question 12 and updated discontinuation rates as per question 15): £118,895 per QALY. Please note that all scenarios presented in question 12 have been applied to this updated company base-case.

Table 23: Updated company base-case ICER (discounted)

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	91,407
PL metreleptin	[redacted]	[redacted]	158,351
Metreleptin overall	[redacted]	[redacted]	118,895

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; *QALY weighting applied

- Updated *ERG base-case ICER*, overall (discounted) (assumptions as per ERG report with updated baseline age-dependent utilities based on UK Tariff): £224,744 per QALY.

Table 24: Updated ERG base-case ICER (discounted)

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL metreleptin	[redacted]	[redacted]	189,520
PL metreleptin	[redacted]	[redacted]	265,558
Metreleptin overall	[redacted]	[redacted]	224,744

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

These updated ICERs should be used for decision-making by the NICE Evaluation Committee. In addition, to explore and minimise the uncertainty regarding the post-discontinuation assumptions applied for haemoglobin A1c (HbA1c), liver benefits, treatment-related quality of life and carer quality of life, a series of scenario analyses of the company's base-case have been presented as part of this response.

Other considerations:	
25. Population indicated for metreleptin include children, are there any additional considerations required?	No additional considerations are required.

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Questions for clinical experts – Pr Tan answers

ID861: Metreleptin for treating lipodystrophy

- **Time**: 13:00-14:30, Friday 21st August
- **Clinician experts:**
  - Professor Tricia Tan
  - Professor Stephen O'Rahilly
- **NICE**:
  - Yelan Guo – technical adviser

Questions & notes:

I. The clinical use of metreleptin in consideration of the current marketing authorisation: Population that would be eligible for treatment

- Which patients with lipodystrophy would be eligible for metreleptin in clinical practice and what criteria would be used when it comes to the eligibility criteria?
- The MA for the use of metreleptin in patients with partial lipodystrophy (PL) is not restrictive. Would you limit its use to a subgroup of patients and if so why? To your knowledge is there any consensus amongst UK experts treating patients with lipodystrophy in this?
- Would you expect that the subgroup of people with PL (defined as HbA1c ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L) would have a different natural history from the overall PL population? Would you expect that the disease defined by the above characteristics would respond differently to metreleptin? Do patients with lower concentrations of leptin follow a different course and would you expect their response to metreleptin to differ from that of the full PL population?

There is no current consensus on the definition of patients with PL eligible for treatment. The criteria (HbA1c ≥6.5% and triglycerides ≥5.65 mmol/L at baseline) used in the NIH follow-up study to define a subgroup of patients were post-hoc, there is no evidence how the treatment effect on this PL subgroup would differ from that for other PL patients.

Need checking the exact treatment eligibility criteria for PL patients in terms of the HbA1c and triglyceride levels for the EAP programme at Endenbrooke hospital, but should be very close to those of the NIH study;

Baseline leptin level <12ng/ml is currently part of EAP's eligibility criteria for people with PL to receive treatment;

Regarding the leptin level at baseline, those who started with lower leptin level will experience a larger treatment effect, however, the relationship between basline leptin level and treatment effect is non-linear; clear definition of leptin level could be challenging in clinical practice.

I note that Prof O'Rahilly has suggested that all patients with GL should be considered for treatment. He has also defined some currently used Addenbrooke's criteria for patients with PL (maximal standard diabetes and lipid treatment, HbA1c >58 mmol/mol and/or fasting TG >5.0 mmol/L, some flexibility around cases of extreme hyperphagia and/or intolerance of standard diabetes treatment). I am supportive of this approach but am concerned that it will be difficult to define 'extreme hyperphagia'.

II. Clinical evidence: representativeness of studies used to inform clinical effectiveness of metreleptin

The NIH study was carried out in the US, there are some differences in clinical practice between it and the EAP study at Addenbrooke hospital, for example, lipid-lowering medications for LP patients:

- In the clinical experts' view, are the populations in the main studies (the NIH study and the GL/PL natural history study, which were used to inform the indirect treatment comparison (ITC)) representative of those seen in UK clinical practice?

I believe this would be reasonably representative of UK clinical practice, but noted that there would be restrictions on PL patients considered for treatment by Addenbrooke's.

- In the clinical experts' view, what is causing the discrepancy in the effects of metreleptin treatment noted (particularly with respect to changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a 12 months change in triglyceride levels from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke's EAP) vs. -10.54 mmol/l (NIH follow-up). Which treatment effect is more likely to be observed in future UK clinical practice?

The discrepancy arises from the fact that the NIH follow-up included patients with a wide range of TG levels. Hence, treatment with leptin would induce a larger absolute change in TG levels compared to the EAP data, which included patients with a relatively restricted range of TG levels.

- Would different criteria be used in the future for patients when it comes to metreleptin treatment than those required for in the EAP and would a different response be expected? If yes, in what way?

Noted that the EAP at Addenbrooke's Hospital started many years ago (year 2005), was not set up as a trial and the criteria currently used were not in place at the beginning of the audit. The measurement of outcomes such as change in HbA1c and triglyceride levels won't be as standardised as in NIH study. Criteria for eligibility for PL patients were set up about 2 years ago in the EAP. In the future the same eligibility criteria will be used but the criterion for baseline leptin level won't be absolutely rigid.

III. The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison (ITC)

No direct comparative data was available for the clinical effectiveness of metreleptin vs. supportive care, what is the experts' view of the relative effectiveness of metreleptin, and the uncertainties associated with the indirect treatment comparison (ITC) undertaken by the company?

- Limited number of covariates were adjusted for in the ITC conducted by the company, are those covariates (namely, age, gender and lipodystrophy type) the most important and relevant for baseline difference adjustment to predict the course of the disease? Would you expect to see the absolute change in HbA1c and triglyceride levels associated with metreleptin treatment vary with baseline HbA1c or triglyceride level?
- Would it be appropriate to use the EAP (Early Access Programme) study, which includes only UK patients at Addenbrooke's Hospital, instead of the NIH study for the ITC?

Baseline HbA1c and triglyceride levels could have an impact on treatment effect of metreleptin, the higher the baseline levels, the larger the treatment effect. Changes in HbA1c and triglyceride levels from baseline associated with metrelpetin treament may be different in absolute terms, but could be the same relatively;

Please see section above for what I was saying about the differences in baseline levels leading to large absolute changes in level with treatment.

As mentioned above, EAP will be less informative and it's more appropriate to use NIH study to inform the ITC.

Because of the limitations of the EAP study mentioned above, we think it more appropriate to use the NIH data.

IV. Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD

Only evidence with a short follow-up time (mostly limited to one-year) is available from the main trials of the company, and there is no evidence available to support

metreleptin's long-term treatment effect on clinically important outcomes such as organ damage of the liver, heart and kidneys, or on the important patient-perceived outcome such as hyperphagia

- What is the experts' view on the long term treatment effect of metreleptin on clinical outcomes such as organ abnormalities (liver, kidney and heart) and female reproductive dysfunction? Is there any reason that these abnormalities and dysfunction would not continue to occur at a rate consistent with future levels of HbA1c and triglycerides while patients are having metreleptin treatment in the longer term?

When giving treatment, what one would really want to focus on is the prevention of hard clinical outcomes such as heart, kidney, and diabetic diseases which HbA1c and triglyceried levels predict. Liver disease too if the liver fat is redueced. Those clinical outcomes could all be mediated if the control on the metabolic measures is sustained;

HbA1c and triglycerid levels are reasonsble surrogate for long-term outcomes in people for lypodsytrophy, however, the overall risk of dying young is still greater for this population. The risk of mortality often comes from diabetes but there is a lack of evidence;

In short, metreleptin could improve surrogate markers for all those clinical outcomes, but patients could still die.

One key problem is that the trials are centered around improvements in surrogate outcomes, mainly:

- HbA1c: will be strongly linked to development of renal disease and less strongly linked to liver and cardiovascular outcomes.
- Triglycerides: will be weakly linked to cardiovascular outcomes and more strongly linked to rates of pancreatitis.
- Liver enzymes: will be weakly linked to rates of liver disease.

However, there is no good marker in the presented studies to predict effects on reproductive dysfuncation. In conclusion, although the improvements in these markers may correlate with improvements in various hard clinical endpoints, the relationship of these markers to the clinical endpoints is not likely to be exactly the same as in ordinary patients with T2DM/metabolic syndrome.

- What is the experts' view on the long term treatment effect of metreleptin on patient reported outcomes such as hyperphagia and quality of life?

Hyperphagia does not happen in isolation. As metrelepin addresses one of the main underlying issues of lipodystrophy, which is leptin deficiency, improvement in leptin deficiency could have a positive effect on hyperphagia, as well as quality of life.

Unfortunately this issue is under-studied in the available clinical data. Metreleptin treatment is likely to reduce hyperphagia, but there is no simple relationship between

eating less or more and quality of life, so the impact of this treatment effect on utility will be difficult to measure.

- There are case reports of neutralizing antibody limiting the effect of metreleptin. Would you expect that to be the case in a significant proportion of treated patients and what impact would be expected on outcomes such as HbA1c and triglycerides in the long term?

Few isolated cases in pateints, in some it comes and goes, hard to know whether it is truly neutralizing antibody;

Rare events, relevant to some but not appeared to be a problem in clinical practice;

Insignificant impact.

Other peptide-based therapies (insulin, GLP-1 etc) are documented to cause the production of anti-drug antibodies and in the main these are not associated with a reduction in efficacy. I think the likelihood of this problem causing issues is low.

- For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume? If yes, by what mechanism? If this is thought likely, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible? And how much?

There would be a bounce-back of HbA1c to its previous level if metreleptin is discontinued; the bounce-back could take about 6 months to 1 year;

The previous reduction in HbA1c level could translate into future benefits, providing some protection for long-term outcomes;

A period of good control confers long term benefits even the HbA1c level shoots back to the original upon treatment discontinuation, or even that control wanes over the years;

In diabetes, short-term control of HbA1c confers long-term benefit and a period of protection, delaying the occurrence of hard clinical outcomes. Eventually the occurrence of hard clinical outcomes would catch up, but unsure how long that would take.

I would emphasise that it is likely that improvements in HbA1c and other metabolic benefits would regress back to the baseline values after discontinuation of metreleptin. This regression is (as mentioned) likely to take place over 6-12 months. Although a period of good metabolic control may confer long-term benefits on clinical outcomes (the so-called ‘metabolic memory’ effect) I would state that this is based on a different clinical context (Type 1 diabetes) and may not apply to this particular context.

- Is there a correlation between surrogate outcomes such as HbA1c and clinical outcomes such as cardiovascular and kidney diseases in people with LD and is this the same as seen in other diseases, for example, diabetes?

HbA1c level is good indicator for cardiovascular, kidney, diabetes, and retinopothy, and neuropathy, for people with lipodystrophy too;

See notes above. The surrogate outcomes used in the studies have some relationship to clinical outcomes, but the relationship varies with the surrogate marker and the particular clinical endpoint. I would, for example, accept a likely strong relationship of HbA1c with kidney disease, retinopathy and neuropathy (as has been shown for T1 and T2 diabetes).

However the relationship of HbA1c to cardiovascular disease, although there is one, is more uncertain and I would caution against assuming that this can be modelled by the experience of T2 diabetes. We have learnt that drug-induced improvements in HbA1c may not translate to decided improvements in cardiovascular and renal disease (e.g. with DPP-IV inhibitors) whereas other drugs that improve HbA1c to the same extent may have outsize impacts on cardiovascular disease and renal disease that go beyond the simple improvement in glycaemia (e.g. with SGLT-2 inhibitors and GLP-1 analogues).

With regards to liver disease, it is not clear to me that any of the markers used (HbA1c, triglycerides, liver enzymes) bear a close relationship to the development of NASH and cirrhosis. This is currently a rather difficult area in hepatology as there are no clear 'gold-standard' markers for this problem.

V. Discontinuation rate of metreleptin treatment

- ~~**For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume?**~~
- ~~**If yes, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible?**~~
- What would be the discontinuation rate on metreleptin treatment in UK clinical practice? Is the 8.93% in year 1, 5.63% in years 2-9 and 2.04% in years 10 onwards, which closely reflects the discontinuation observed in the first year of the NIH trial and the decline in discontinuation over time, plausible?

Reasonable estimates for discontinuation.

VI. Assumptions in the model: baseline transition probabilities and pathway through organ sub-models

In the company's model, patient transitions between states of each of the sub-models were mostly determined by transition probabilities from the literature, in populations relevant to each sub-model condition, which were adjusted using

surrogate outcomes such as HbA1c, AST\ALT to account for the reduction in risk of organ complications associated with metreleptin.

- Is it appropriate to assume that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but caused by different underlying diseases, and therefore patients with lipodystrophy will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions but caused by different underlying disease states?

Reasonable, using transition probabilities from those disease areas won't over-esimate that for lypodsystrophy but may under-esimate;

Specific features of lipodystrophy that could worsen the outcomes may not be captured.

Unfortunately I do not see any alternative approach to modelling any anticipated clinical improvements from previous experience from other metabolic diseases such as T2DM and non-alcoholic fatty disease. It is likely, however, that the special case of lipodystrophy is more likely to accentuate the adverse clinical outcomes from the identified metabolic dysfunctions, but how much accentuation really exists cannot be estimated from the available data.

It should also be noted that unique features of lipodystrophy (cosmetic, hyperphagia issues) may not be adequately captured by modelling against the other common metabolic disease.

VII. Metreleptin's continued treatment effect on HbA1c post-discontinuation

There is no evidence on metreleptin's continued treatment effect on outcomes including HbA1c levels, liver disease, and quality of life post discontinuation – data was not presented in the clinical section of the submission. In the company's model, the absolute change in HbA1c from baseline to 12 months associated with metreleptin was used to adjust the baseline transition probabilities to generate probabilities for the metreleptin cohort in the cardiovascular, kidney, neuropathy and retinopathy sub-models.

In the first cycle of the model, patients receiving metreleptin experienced the full reduction in their HbA1c levels observed at 12 months of NIH study. After that in every cycle all patients in the model received an annual increase in HbA1c of 0.15%, regardless of whether they are on treatment with metreleptin, have discontinued from metreleptin or are receiving SC. In other words, discontinuation of metreleptin was assumed to have no impact on its efficacy in the four organ sub-models using HbA1c to determine transition probabilities, because patients have received the full benefit of metreleptin in terms of HbA1c reduction and HbA1c rises at the same rate as patients taking supportive care from after the 1st cycle.

- (1st part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?
- Is it appropriate to assume that, post-discontinuation of metreleptin treatment, the relative efficacy of metreleptin compared with supportive care would remain constant over the life time, and the change in HbA1c level will be the same in the metreleptin and supportive care groups?

Discontiuation of metrelptin would have an impact on HbA1c level. It would return to its previous level. However, pevious reduction translates into future outcomes by providing protection to clinical outcomes;

A period of good control confers long term benefits, even the HbA1c level returns to its original after discontinuation of metreleptin treatment;

Once bounce back to its original (taking about 6 months to 1 year) after the stopping of treatment, the change in HbA1c level will be the same in metreleptin and supportive care arms.

I think it is unreasonable to assume that Metreleptin has a permanent salutary effect on HbA1c, triglycerides etc if discontinued, as discussed above this is likely to regress to baseline over 6-12 months. The slope of the HbA1c curve in treatment discontinuers will jump up and rejoin the curve of the HbA1c curve in best supportive care.

VIII. Metreleptin's continued treatment effect on liver complications post discontinuation

- (2nd part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on ~~**HbA1c**~~ **ALT/AST** level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?

ALT/AST are not good indicators for any outcomes. Liver fat level could be a better indicator for liver disease. Similarly, liver fat level could rapidly return to its original, but the change will be the same as those receiving supportive care after the bounce-back;

Unsure about how long this bounce-back of liver fat would take in liver disease.

AST/ALT are not good indicators for liver disease, as there are plenty of patients with T2DM and known fatty liver disease who have apparently normal AST/ALT. The underlying question will be whether discontinuation of Metreleptin leads to long-term advantage over best supportive care and this is implausible, although the time taken to come back to baseline risks of transitioning to higher grades of liver disease is uncertain.

IX. Sources of utility values and assumptions around additional utilities used in the model

- Is it appropriate to use utility values from the literature based on populations with disorders other than LD, on which the sub-models are based and apply them to LD populations at the same state in the model?

Reasonable, but utility values for lypodsystrophy may be a bit under-estimated.

As noted above, there does not seem to be any more reasonable way of modelling this. I note that there is no specific adjustment for utility in terms of the special symptoms of lipodystrophy except for an 'other symptoms' decrement of -0.22 which is effectively plucked out of the air. I think however that this is in keeping with clinical experience and the disutilities of other conditions in Table 35.

X. Number of carers

- On average, how many carers are needed for the caring of a person with LD and will this change throughout their lifetime e.g. more or fewer as people reach adulthood?

Difficult to estimate, patient groups may be in a better position to comment;

Many adults may not need carer, but caring will be needed when they get seriously sick, it depends.

Questions for clinical experts – Pr O'Rahilly answers

ID861: Metreleptin for treating lipodystrophy

- **Time**: 13:00-14:30, Friday 21st August
- **Clinician experts:**
  - Professor Tricia Tan
  - Professor Stephen O'Rahilly
- **NICE**:
  - Yelan Guo – technical adviser

Before responding to the specific questions asked it may be helpful for me to provide an overview, derived from discussion between myself and my colleagues Profesor David Savage and Dr Anna Stears who run the natonal service for lipodystrophy, of our thoughts about two questions which are germane to many of the questions that are arising

Who should receive Metreleptin?

1. All people with CL should receive leptin therapy and this will be a life long therapy except in those unable, for whatever reason, to tolerate it or to comply with necessary supervision
2. Patients with PL and the metabolic criteria specified below should receive metreleptin. If this results in insufficient metabolic benefits within 9 months it should be stopped
3. If there is some metabolic benefit (but less than the specified threshold) but other features have improved markedly (hyperphagia, number of other medicines, fatty liver) then a further period on leptin before reassessing is warranted
4. Patients currently on the extended access programme who report benefit and wish to continue should be allowed to continue

What are the long term impacts of metreleptin on those who discontinue

5. If patents discontinue for whatever reason the benefits to their long term health will persist to a degree proportional to the **extent and duration** of the reduction of risk factors including glucose (as reflected by HbA1c), which is critical for neuropathy, retinopathy and nephropathy, and important for macrovascular health (CV events); liver fat, which is critical for cirrhosis, and circulating insulin, which likely contributes to CV events and possibly to liver disease and nephropathy
6. Patients who are obtaining benefit but discontinue metreleptin will show a rapid return of hyperphagia (days), liver fat (weeks), HbA1c (months)

7. Patients who discontinue because there is no discernible metabolic benefit are unlikely to show any long term benefit in their health outcomes attributable to the period of metreleptin treatment

Questions & notes:

I. The clinical use of metreleptin in consideration of the current marketing authorisation: Population that would be eligible for treatment

- Which patients with lipodystrophy would be eligible for metreleptin in clinical practice and what criteria would be used when it comes to the eligibility criteria?

  All patients with confirmed (by genetic testing or specialist clinical opinion where this is not available or the causative gene is unknown) generalised lipodystrophy >2 years of age

  See below re PLD

- The MA for the use of metreleptin in patients with partial lipodystrophy (PL) is not restrictive. Would you limit its use to a subgroup of patients and if so why? To your knowledge is there any consensus amongst UK experts treating patients with lipodystrophy in this?

  Yes. We would advocate the following:

1. Confirmed partial lipodystrophy (age over 12 years)
2. Maximal standard anti-diabetic and lipid lowering therapies including insulin therapy
3. HbA1c>7.5% (58mmol/mol) and/or fasting triglycerides >5.0mmol/l. The HbA1c criteria to be lower under exceptional circumstances, such as extreme hyperphagia and/or severe side effects from other glucose lowering medications

These are broadly agreed across the UK and EU

- Would you expect that the subgroup of people with PL (defined as HbA1c ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L) would have a different natural history from the overall PL population? Would you expect that the disease defined by the above characteristics would respond differently to metreleptin? Do patients with lower concentrations of leptin follow a different course and would you expect their response to metreleptin to differ from that of the full PL population?

It is diffciukt to answer the first question. The most likely scenario is that these people are presenting at a later point in the time course of the natural history, compared to those who present with with less severe metabolic derangement

Regarding the leptin level at baseline, those who started with lower leptin level may experience a larger treatment effect, however, the relationship between basline leptin

level and treatment effect is non-linear; clear definition of a “cut off” leptin level could be challenging in clinical practice.

II. Clinical evidence: representativeness of studies used to inform clinical effectiveness of metreleptin

The NIH study was carried out in the US, there are some differences in clinical practice between it and the EAP study at Addenbrooke hospital, for example, lipid-lowering medications for LP patients:

- In the clinical experts’ view, are the populations in the main studies (the NIH study and the GL/PL natural history study, which were used to inform the indirect treatment comparison (ITC)) representative of those seen in UK clinical practice?

  Yes

- In the clinical experts’ view, what is causing the discrepancy in the effects of metreleptin treatment noted (particularly with respect to changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a 12 months change in triglyceride levels from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke’s EAP) vs. -10.54 mmol/l (NIH follow-up). Which treatment effect is more likely to be observed in future UK clinical practice?

  The EAP was largely based on ‘compassionate use’ rather than formal clinical criteria. Many of the patients would not meet the proposed criteria which have developed over time.

- Would different criteria be used in the future for patients when it comes to metreleptin treatment than those required for in the EAP and would a different response be expected? If yes, in what way?

Note that the EAP at Addenbrooke’s hospital started many years ago (year ~2008), was not set up as a trial and those criteria currently used were not in place at the beginning or in earlier years; Some Uk patients had also gone over to the USA prior to this data – 2002-2004 and were already on metreleptin – they were then taken over at our centre

It was a compassionate programme, did not use the same criteria as what’s being used today and measurement of outcomes such as change in HbA1c and triglyceride levels won’t be as standard as in NIH study;

The criteria for PL patients eligible for treatment were set up about 2 years ago in the EAP. In the future the same eligibility criteria would be used, We will measure baseline leptin levels and anticpate that those with lower levels will response more but we will not use a rigid baseline criterion

The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison (ITC)

No direct comparative data was available for the clinical effectiveness of metreleptin vs. supportive care, what is the experts' view of the relative effectiveness of metreleptin, and the uncertainties associated with the indirect treatment comparison (ITC) undertaken by the company?

- Limited number of covariates were adjusted for in the ITC conducted by the company, are those covariates (namely, age, gender and lipodystrophy type) the most important and relevant for baseline difference adjustment to predict the course of the disease?

Yes these seem reasonable

- Would you expect to see the absolute change in HbA1c and triglyceride levels associated with metreleptin treatment vary with baseline HbA1c or triglyceride level?
- Would it be appropriate to use the EAP (Early Access Programme) study, which includes only UK patients at Addenbrooke's Hospital, instead of the NIH study for the ITC?

Baseline HbA1c and triglyceride levels could have an impact on treatment effect of metreleptin, the higher the baseline levels, the larger the treatment effect. Changes in HbA1c and triglyceride levels from baseline associated with metrelpetin treament may be different in absolute terms, but could be the same relatively;

As mentioned above, EAP will be less informative and it's more appropriate to use NIH study to inform the ITC.

III. Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD

Only evidence with a short follow-up time (mostly limited to one-year) is available from the main trials of the company, and there is no evidence available to support metreleptin's long-term treatment effect on clinically important outcomes such as organ damage of the liver, heart and kidneys, or on the important patient-perceived outcome such as hyperphagia

The NIH team have been using leptin since around 2000 so this is not strictly true – many patients should have follow up data for many years.

- What is the experts' view on the long term treatment effect of metreleptin on clinical outcomes such as organ abnormalities (liver, kidney and heart) and female reproductive dysfunction? Is there any reason that these abnormalities and

dysfunction would not continue to occur at a rate consistent with future levels of HbA1c and triglycerides while patients are having metreleptin treatment in the longer term?

When giving treatment, what one would really want to focus on is the prevention of hard clinical outcomes such as heart, kidney, and diabetic diseases which HbA1c and triglyceried levels predict. Liver disease too if the liver fat is redueced. Those clinical outcomes could all be delayed or alleviated if the control on the metabolic measures is sustained;

HbA1c and triglyceride levels are reasonable surrogates for long-term outcomes in people with lipodsytrophy, however, the overall risk of dying young is probably still greater for this population. Diabetes is an important factor in increasing the risk of early mortality but there are other factors too such as sustained hyperinsulinaemia – some of these would be alleviated by leptin therapy but some may not be.

In short, metreleptin could improve surrogate markers for all those clinical outcomes, but patients could still die, though one would expect leptin to reduce mortality in line with the improvements in Hba1c and TGs.

- What is the experts' view on the long term treatment effect of metreleptin on patient reported outcomes such as hyperphagia and quality of life?

Hyperphagia does not happen in isolation. As metrelepin addresses one of the main underlying issues of lipodystrophy, which is leptin deficiency, improvement in leptin deficiency could have a positive effect on hyperphagia, as well as quality of life. Importantly, although leptin has been reported to do so and would certainly be expected to improve hyperphagia, hyperphagia was not formally assessed in many of the patients treated at the NIH so there is very little definitive data on this issue. However, it is very well established that very low leptin levels have a major impact on hyperphagia so leptin therapy is very likely to affect it in patients with generalised and to a lesser extent partial LD.

- There are case reports of neutralizing antibody limiting the effect of metreleptin. Would you expect that to be the case in a significant proportion of treated patients and what impact would be expected on outcomes such as HbA1c and triglycerides in the long term?

There have been a few isolated cases, in some it comes and goes, It is often difficult to know whether it is truly neutralizing antibody;

These are rare events, relevant to some but have not appeared to be a frequent problem in clinical practice;

This is not considered a major issue by clinicians using metreleptin. The presence of leptin antibodies (neutralising or not) does interfere with leptin measurements in patients on leptin therapy but very seldom has any impact on clinical responses. Nevertheless, it is likely that occasional patients treated with leptin will develop neutralising Abs, so this should be monitored once the therapy is approved.

- For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume? If yes, by what mechanism? If this is thought likely, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible? And how much?

There would be a bounce-back of HbA1c to its previous level if metreleptin is discontinued; the bounce-back could take about 6 months to 1 year;

The previous reduction in HbA1c level could translate into future benefits, providing some protection for long-term outcomes;

A period of good control confers long term benefits even if the HbA1c level shoots back to the original upon treatment discontinuation, or even if control wanes over the years;

In diabetes, short-term control of HbA1c confers long-term benefit and a period of protection, delaying the occurrence of hard clinical outcomes. Eventually the occurrence of hard clinical outcomes would catch up, but it is difficukt to be sure how long that would take.

- Is there a correlation between surrogate outcomes such as HbA1c and clinical outcomes such as cardiovascular and kidney diseases in people with LD and is this the same as seen in other diseases, for example, diabetes?

People with LD will likely develop the compllications of diabetes which are most closely related to chronically elevated blood glucose (reflected by HbA1c) i.e neuropathy, retinopathy at a similar rate to patienst with other causes of their diabetes

Pwopel with LD may develop kidney failiure at a somewhat acclereated rate compared to people with other types of diabetes because lipodystrophy appears to be confer a glucose independent stress on the kidney

People with LD are likely to develop macrovascular disease and cardiovascular events at an accelerated rate compared ot people with other forms of diabetes because as well as chronically high glucose people with LD have very high levels of insulin, which may accelerate atheroma and contribute to heart failure

People wioth LD will develop Chronic end stage liver disease at a much higher rate than people with other foms of diabetes. They are also likely to have more rapidly progressive liver damage than patients with other forms of NASH, as they lack an ability to deposit any extra calories in fat tissues and therefore will contnuwe to deposit fat in the liver throughout their life ;

IV. Discontinuation rate of metreleptin treatment

- ~~For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume?~~
- ~~If yes, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible?~~
- What would be the discontinuation rate on metreleptin treatment in UK clinical practice? Is the 8.93% in year 1, 5.63% in years 2-9 and 2.04% in years 10 onwards, which closely reflects the discontinuation observed in the first year of the NIH trial and the decline in discontinuation over time, plausible?

Discontuation in the NIH trial, at least in some cases, may have related to difficulties patients had in getting to NIH Bethesda,Maryland regularly for assessment. Also, patienst started on treatment who had reanably good metabolic control anyway are less likely to persist. If the starting and stopping criteria we propose are use we anticipate a somewhat lower discontinuation rate

V. Assumptions in the model: baseline transition probabilities and pathway through organ sub-models

In the company's model, patient transitions between states of each of the sub-models were mostly determined by transition probabilities from the literature, in populations relevant to each sub-model condition, which were adjusted using surrogate outcomes such as HbA1c, AST\ALT to account for the reduction in risk of organ complications associated with metreleptin.

- Is it appropriate to assume that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but caused by different underlying diseases, and therefore patients with lipodystrophy will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions but caused by different underlying disease states?

Reasonable, using transition probabilities from those disease areas won't over-esimate that for lypodsystrophy but may under-esimate;

Specific features of lipodystrophy that could worsen the outcomes may not be captured.

VI. Metreleptin's continued treatment effect on HbA1c post-discontinuation

There is no evidence on metreleptin's continued treatment effect on outcomes including HbA1c levels, liver disease, and quality of life post discontinuation – data was not presented

in the clinical section of the submission. In the company's model, the absolute change in HbA1c from baseline to 12 months associated with metreleptin was used to adjust the baseline transition probabilities to generate probabilities for the metreleptin cohort in the cardiovascular, kidney, neuropathy and retinopathy sub-models.

In the first cycle of the model, patients receiving metreleptin experienced the full reduction in their HbA1c levels observed at 12 months of NIH study. After that in every cycle all patients in the model received an annual increase in HbA1c of 0.15%, regardless of whether they are on treatment with metreleptin, have discontinued from metreleptin or are receiving SC. In other words, discontinuation of metreleptin was assumed to have no impact on its efficacy in the four organ sub-models using HbA1c to determine transition probabilities, because patients have received the full benefit of metreleptin in terms of HbA1c reduction and HbA1c rises at the same rate as patients taking supportive care from after the 1st cycle.

- (1st part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?
- Is it appropriate to assume that, post-discontinuation of metreleptin treatment, the relative efficacy of metreleptin compared with supportive care would remain constant over the life time, and the change in HbA1c level will be the same in the metreleptin and supportive care groups?

Discontiuation of metrelptin would have an impact on HbA1c level. It would return to its previous level. However, previous reduction translates into future outcomes by providing protection to clinical outcomes;

A period of good control confers long term benefits, even the HbA1c level returns to its original after discontinuation of metreleptin treatment;

Once it returns to to its original level (taking about 6 months to 1 year) after the stopping of treatment, the change in HbA1c level will be the same in metreleptin and supportive care arms.

VII. Metreleptin's continued treatment effect on liver complications post discontinuation

- (2nd part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on ~~**HbA1c**~~ **ALT/AST** level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?

ALT/AST are not good indicators for any outcomes. Liver fat level could be a better indicator for liver disease. Similarly, liver fat level could rapidly return to its original, but the change will be the same as those receiving supportive care after the bounce-back;

Unsure about how long this bounce-back of liver fat would take in liver disease.

VIII. Sources of utility values and assumptions around additional utilities used in the model

- Is it appropriate to use utility values from the literature based on populations with disorders other than LD, on which the sub-models are based and apply them to LD populations at the same state in the model?

Reasonable, but utility values for lypodsystrophy may be a bit under-estimated.

IX. Number of carers

- On average, how many carers are needed for the caring of a person with LD and will this change throughout their lifetime e.g. more or fewer as people reach adulthood?

Difficult to estimate, patient groups may be in a better position to comment;

Many adults may not need carer, but caring will be needed when they get seriously sick.

Questions for clinical experts – Dr Stears answers

ID861: Metreleptin for treating lipodystrophy

I. The clinical use of metreleptin in consideration of the current marketing authorisation: Population that would be eligible for treatment

- Which patients with lipodystrophy would be eligible for metreleptin in clinical practice and what criteria would be used when it comes to the eligibility criteria?

  Please see our suggested starting criteria – already submitted in our response April 2020

NSIR Service suggested guidance for starting and stopping metreleptin treatment

A specialist service review is mandatory pre metreleptin start and at 3,6,9,12,18 and 24 months post start and at least annually thereafter.

1. **Generalised lipodystrophy**

Suggested starting criteria generalised lipodystrophy

A specialist service review is mandatory pre metreleptin start

Starting criteria as specified in the therapeutic indications:

1. Confirmed generalised lipodystrophy (age over 2 years)
2. Attendance of dietary education session

No additional metabolic criteria

Suggested stopping criteria generalised lipodystrophy

At 6-9 months after starting metreleptin or anytime thereafter – after specialist service review

Stop metreleptin therapy if poor compliance/non-engagement with appointments

No metabolic stopping criteria

2. **Partial lipodystrophy**

Suggested starting criteria partial lipodystrophy

A specialist service review is mandatory pre metreleptin start

To start metreleptin therapy **all** criteria below must be met:

1. Confirmed partial lipodystrophy (age over 12 years)
2. Attendance of dietary education session

3. Maximal standard anti-diabetic and lipid lowering therapies including insulin therapy
4. HbA1c>7.5% (58mmol/mol) and/or fasting triglycerides >5.0mmol/l
5. Leptin concentration < 10ng/ml

Suggested stopping criteria partial lipodystrophy

At 6-9 months after starting metreleptin – specialist service review

1. Stop metreleptin therapy if there is poor compliance/non-engagement with appointments

2. Stop metreleptin therapy if there has NOT been an HbA1c reduction of at least 0.5% from baseline (eg from 8.0 to 7.5%, or 9.0 to 8.5%) or a fall in fasting triglycerides of at least 50% from baseline.

NB: The specialist service may agree to continue leptin therapy in occasional patients with partial lipodystrophy who have not met the above metabolic criteria but who are judged by the specialist service to have had other significant treatment benefits such as a very significant reduction in concomitant medication, significant improvement in fatty liver disease, and/or a significant improvement in quality of life due to for example a significant appetite reduction, or in whom a trial of dose escalation is thought to be required.

- The MA for the use of metreleptin in patients with partial lipodystrophy (PL) is not restrictive. Would you limit its use to a subgroup of patients and if so why? To your knowledge is there any consensus amongst UK experts treating patients with lipodystrophy in this?

See above for suggested starting criteria. There are no other centres in the UK permitted to prescribe metreleptin. These criteria have been broadly accepted across European lipodystrophy centres.

- Would you expect that the subgroup of people with PL (defined as HbA1c ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L) would have a different natural history from the overall PL population?

  No- I would expect the natural history to be the same in this subgroup.

- Would you expect that the disease defined by the above characteristics would respond differently to metreleptin?

  No, but minimal improvement of the HbA1c would be expected in patients with HbA1c of 6.5mmol/mol-7.5mmol/mol as this shows very good baseline blood glucose control

  Do patients with lower concentrations of leptin follow a different course and would you expect their response to metreleptin to differ from that of the full PL population?

  Possibly PL patients with a lower leptin concentration do better than those with a higher leptin concentration but there is no definitive trial evidence for this.

II. Clinical evidence: representativeness of studies used to inform clinical effectiveness of metreleptin

The NIH study was carried out in the US, there are some differences in clinical practice between it and the EAP study at Addenbrooke hospital, for example, lipid-lowering medications for LP patients:

- In the clinical experts' view, are the populations in the main studies (the NIH study and the GL/PL natural history study, which were used to inform the indirect treatment comparison (ITC)) representative of those seen in UK clinical practice?

  Yes

- In the clinical experts' view, what is causing the discrepancy in the effects of metreleptin treatment noted (particularly with respect to changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a 12 months change in triglyceride levels from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke's EAP) vs. -10.54 mmol/l (NIH follow-up). Which treatment effect is more likely to be observed in future UK clinical practice?

  The EAP was not a research study. The patients received metreleptin as part of a compassionate use programme. The data was that collected in routine clinical practice with retrospective data collation from clinical records. This was incomplete for some patients as we do not have access to metabolic data from other health care settings.There are insufficient patient numbers and the patient population for PL did not have poor enough metabolic status at baseline to be representative of the effect of metreleptin.

  The EAP data contains very few GL patients' response to metreleptin so general conclusion regarding efficacy cannot be made from this data.

  PL patients with good baseline metabolic control were included in EAP who would not be likely to be offered metreleptin therapy in the future

- Would different criteria be used in the future for patients when it comes to metreleptin treatment than those required for in the EAP and would a different response be expected? If yes, in what way?

  Yes – see proposed starting criteria above. A more marked metabolic improvement would be expected with metreleptin therapy in PL patients who have a worse baseline metabolic status than in those with normal HbA1c/Tg at baseline.

III. The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison (ITC)

No direct comparative data was available for the clinical effectiveness of metreleptin vs. supportive care, what is the experts' view of the relative effectiveness of metreleptin, and the uncertainties associated with the indirect treatment comparison (ITC) undertaken by the company?

- Limited number of covariates were adjusted for in the ITC conducted by the company, are those covariates (namely, age, gender and lipodystrophy type) the most important and relevant for baseline difference adjustment to predict the course of the disease?

  Yes these are acceptable co-variates.

- Would you expect to see the absolute change in HbA1c and triglyceride levels associated with metreleptin treatment vary with baseline HbA1c or triglyceride level?

  Yes - A more marked metabolic improvement would be expected with metreleptin therapy in PL patients who have a worse baseline metabolic status than in those with normal HbA1c/Tg at baseline.

- Would it be appropriate to use the EAP (Early Access Programme) study, which includes only UK patients at Addenbrooke's Hospital, instead of the NIH study for the ITC?

  No –**The EAP was not a research study**. It was a compassionate use programme. The data was collected in routine clinical practice with retrospective data collection from clinical records. There are insufficient patient numbers and the patient population for PL did not have poor enough metabolic status at baseline to reflect the potential treatment effect of metreleptin. The NIH studies were clinical trials and the data from these is more robust.

IV. Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD

Only evidence with a short follow-up time (mostly limited to one-year) is available from the main trials of the company, and there is no evidence available to support metreleptin's long-term treatment effect on clinically important outcomes such as organ damage of the liver, heart and kidneys, or on the important patient-perceived outcome such as hyperphagia

- What is the experts' view on the long term treatment effect of metreleptin on clinical outcomes such as organ abnormalities (liver, kidney and heart) and female reproductive dysfunction?

  There is published data showing an improvement in fatty liver with metreleptin therapy. It is not clear whether the risk of liver cirrhosis/ HCC is reduced but this seems likely.

  There is published data showing an improvement in proteinuria with metreleptin therapy.

  There is published data showing an improvement in reproductive status in women with metreleptin therapy.

  It is likely that if blood glucose and lipid control is improved with metreleptin treatment that there will be a reduction in macrovascular and microvascular complications which are associated with diabetes.

  It is unclear if metreleptin therapy has any direct effect on the organs.

- Is there any reason that these abnormalities and dysfunction would not continue to occur at a rate consistent with future levels of HbA1c and triglycerides while patients are having metreleptin treatment in the longer term?

  I am sorry I do not understand this question

- What is the experts' view on the long term treatment effect of metreleptin on patient reported outcomes such as hyperphagia and quality of life?

  In our experience and the opinion expressed by the patients and their families metreleptin therapy usually improves (reduces) hyperphagia and improves quality of life

- There are case reports of neutralizing antibody limiting the effect of metreleptin. Would you expect that to be the case in a significant proportion of treated patients and what impact would be expected on outcomes such as HbA1c and triglycerides in the long term?

  This has not been a problem for our patients. Sometimes neutralising antibodies do not affect the efficacy of a drug.

- For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume?

- Hyperphagia- no long term benefit would be expected if metreleptin is stopped the symptoms will probably return after a few days
- HbA1c- this will rise after a few weeks of metreleptin is stopped

- Some sustained slowing of liver damage/kidney/macrovascular disease may be maintained for some months after metreleptin is stopped
- It would be preferable if the patient continue treatment long term.
- If yes, by what mechanism? If this is thought likely, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible? And how much?
- Is there a correlation between surrogate outcomes such as HbA1c and clinical outcomes such as cardiovascular and kidney diseases in people with LD and is this the same as seen in other diseases, for example, diabetes?

  There is no data but this is a reasonable assumption. Patients with lipodystrophy treated with metreleptin would be expected to have additional improvements in fatty liver and macrovascular disease due to improvement in hyperinsulinaemia.

V. Discontinuation rate of metreleptin treatment

- For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume?

  Repeated question
- If yes, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible?
- Repeated question
- What would be the discontinuation rate on metreleptin treatment in UK clinical practice? Is the 8.93% in year 1, 5.63% in years 2-9 and 2.04% in years 10 onwards, which closely reflects the discontinuation observed in the first year of the NIH trial and the decline in discontinuation over time, plausible?

  Yes

VI. Assumptions in the model: baseline transition probabilities and pathway through organ sub-models

In the company's model, patient transitions between states of each of the sub-models were mostly determined by transition probabilities from the literature, in populations relevant to each sub-model condition, which were adjusted using surrogate outcomes such as HbA1c, AST\ALT to account for the reduction in risk of organ complications associated with metreleptin.

Is it appropriate to assume that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but caused by different underlying diseases, and

therefore patients with lipodystrophy will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic conditions but caused by different underlying disease states?

Yes in general this is a reasonable assumption but patients with lipodystrophy treated would be expected to have a more severe course of morbidity especially in progression of fatty liver and macrovascular disease and episodes of pancreatitis due to hyperinsulinaemia and severe hyperglycaemia and lipid abnormalities.

VII. Metreleptin's continued treatment effect on HbA1c post-discontinuation

There is no evidence on metreleptin's continued treatment effect on outcomes including HbA1c levels, liver disease, and quality of life post discontinuation – data was not presented in the clinical section of the submission. In the company's model, the absolute change in HbA1c from baseline to 12 months associated with metreleptin was used to adjust the baseline transition probabilities to generate probabilities for the metreleptin cohort in the cardiovascular, kidney, neuropathy and retinopathy sub-models.

In the first cycle of the model, patients receiving metreleptin experienced the full reduction in their HbA1c levels observed at 12 months of NIH study. After that in every cycle all patients in the model received an annual increase in HbA1c of 0.15%, regardless of whether they are on treatment with metreleptin, have discontinued from metreleptin or are receiving SC. In other words, discontinuation of metreleptin was assumed to have no impact on its efficacy in the four organ sub-models using HbA1c to determine transition probabilities, because patients have received the full benefit of metreleptin in terms of HbA1c reduction and HbA1c rises at the same rate as patients taking supportive care from after the 1st cycle. (please define a 'cycle')

- (1st part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?

  No I do not think this is appropriate. If metreleptin is discontinued I would expect the HbA1c to rise to baseline or above within a few months.

- Is it appropriate to assume that, post-discontinuation of metreleptin treatment, the relative efficacy of metreleptin compared with supportive care would remain constant over the life time, and the change in HbA1c level will be the same in the metreleptin and supportive care groups?

  No I do not think this is appropriate. If metreleptin is discontinued I would expect the HbA1c to rise to baseline or above within a few months.

VIII. Metreleptin's continued treatment effect on liver complications post discontinuation

- (2nd part of question) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?

  A repeat of question above

IX. Sources of utility values and assumptions around additional utilities used in the model

- Is it appropriate to use utility values from the literature based on populations with disorders other than LD, on which the sub-models are based and apply them to LD populations at the same state in the model?

  I do not fully understand this question, as the types of other disorders and sub-models are not specified in the question- but patients with lipodystrophy would be expected to have a severe course of morbidity especially in progression of fatty liver and macrovascular disease and episodes of pancreatitis due to hyperinsulinaemia and severe hyperglycaemia and lipid abnormalities.

X. Number of carers

- On average, how many carers are needed for the caring of a person with LD and will this change throughout their lifetime e.g. more or fewer as people reach adulthood?

  Each patient is different. The term 'carers' needs to be defined for an accurate answer to this question.

  Children with LD need carers (parents/teachers) and some, but not all may need support with learning difficulties.

  Adults with LD are usually independent if they are clinically well and if they do not have learning disability but if they develop complications, eg stroke, blindness, amputation, they will need carers

NICE National Institute for Health and Care Excellence

Technical engagement response form

Metreleptin for treating lipodystrophy [ID861]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm, 9 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text:

'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Lipodystrophy UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: The clinical use of metreleptin in consideration of its current markeing authorisation/ Population that would be eligible for treatment	
1. Which patients with lipodystrophy would be eligible for metreleptin in clinical practice and what criteria would be used when it comes to the eligibility criteria?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
2. The MA for the use of metreleptin in patients with partial lipodystrophy (PL) is not restrictive. Would you limit its use to a subgroup of patients and if so why? To your knowledge is there any consensus amongst UK experts treating patients with lipodystrophy in this?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
3. Would you expect that the subgroup of people with PL (defined as HbA1c ≥6.5% and/or baseline levels of triglycerides ≥5.65 mmol/L) would have a different natural history from the overall PL population? Would you expect that the disease defined by the above characteristics wouldrespond differently to metreleptin? Do patients with lower concentrations of leptin follow a different course and would you expect their response to metreleptin to differ from that of the full PL population?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation

Issue 2: Representativeness of studies used to inform clinical effectiveness of metreleptin	
4. Are the populations in the main studies (the NIH study and the GL/PL natural history study) which were used to inform the indirect treatment comparison representative of those seen in UK clinical practice?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
5. What is causing the discrepancy in the effects of metreleptin treatment noted (particularly with respect to changes in triglyceride levels) between the EAP data and the NIH 991265/20010769 study and also the NIH follow-up study that was used in the ITC. For example, for GL patients there was a 12 months change in triglyceride levels from 6.4 to 4.1 (about -2.3) mmol/l (Addenbrooke's EAP) vs. -10.54 mmol/l (NIH follow-up). Which treatment effect is more likely to be observed in future UK clinical practice?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
6. Would different criteria be used in the future for patients when it comes to metreleptin treatment than those required for in the EAP and would a different response be expected? If yes, in what way?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
Issue 3: The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison	
7. Limited number of covariates were adjusted for in the ITC conducted by the company, are those covariates (namely, age, gender and lipodystrophy type) the most important and	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation

relevant for baseline difference adjustment to predict the course of the disease? Would stakeholders expect to see the absolute change in HbA1c and triglyceride levels associated with metreleptin treatment vary with baseline HbA1c or triglyceride level?	
8. Would it be appropriate to use the EAP (Early Access Programme) study, which includes only UK patients at Addenbrooke's Hospital, instead of the NIH study for the ITC?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
Issue 4: Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD	
9. What is the stakeholder's view on the long term treatment effect of metreleptin on clinical outcomes such as organ abnormalities (liver, kidney and heart) and female reproductive dysfunction? Is there any reason that these abnormalities and dysfunction would not continue to occur at a rate consistent with future levels of HbA1c and triglycerides while patients are having metreleptin treatment in the longer term?	From the patient viewpoint, the long-term treatment effect of metreleptin has so far been, and would continue to be, to slow down the development and reduce the severity of organ abnormalities, providing many additional years of good quality of life. In particular, through discussions with the lipodystrophy community, we have several reports of patients who previously suffered with chronic pancreatitis, with multiple instances leading to hospitalisation, who since starting metreleptin treatment have had no further instances of pancreatitis. In terms of female reproductive dysfunction, we have many reports where the application of metreleptin treatment has resulted in a return to normal menstruation patterns. Below are some of the responses obtained during the Living with Lipodystrophy Community Survey [developed and collated by Lipodystrophy UK (2020) and submitted as part of the HST Patient carer organisation submission (May 2020)], when asked 'What benefits have you/the patient experienced from [metreleptin] treatment?'

	“Triglycerides back to normal, appetite back to normal, no more fatty liver” “Appetite suppression, stable blood fats, delayed liver deterioration” “My fatty liver has gone down considerably as when it was first enlarged it was very uncomfortable” “I feel in general it helps different aspects of my mental and physical health. If I wasn’t on it I think I would have been in hospital more times with pancreatitis, since being on Leptin I have not had one episode.” “Significant improvements in hyperphagia, significant improvement in immune system, significant improvement in fatty liver, improvement in triglycerides and HbA1c” “Diabetic control is now perfect and requires no diabetic medicine or input. Mixed hyperlipidaemia again now within normal limits form being extremely and dangerously high despite medicine and restricted diet.” “Preventing further fat build up in her coronary arteries, which she could not tolerate.” “Fatty liver has improved” “A lot less pancreatitis” “Incredible. My hunger disappeared almost over night. The fat in my liver reduced by over 75%.

	My insulin requirements were cut in half"
10. What is the stakeholder's view on the long term treatment effect of metreleptin on patient reported outcomes such as hyperphagia and quality of life?	With regards to quality of life and hyperphagia, there have been tremendous benefits reported throughout the patient population. As above, the following statements have been taken from the survey responses when asked 'What benefits have you/the patient experienced from [metreleptin] treatment?' "Feeling satisfied by food for the first time in my life." "The hunger issues I had to begin with have improved a lot I used to be very hungry all the time even though I had eaten I would immediately feel hungry again now I don't get that feeling" "It helps keep my weight under control. When I've been off the Leptin for a short period of time I have put weight on and when I have returned to normal use I find my weight is manageable" "Life changing! It allows me more freedom as I no longer have to [inject] huge amounts of Insulin daily. It has kept my weight down so no yo-yoing. It has been very liberating as most of my Lipo health issues have been easily controlled." "Extreme hunger has lessened" "Diabetes is under control so I no longer require conventional diabetes medication" "The fat build up in the chin area has now gone. The constant hunger issue has resolved."

	"I don't feel hungry all the time" "Diabetes easier to control" As a result of these benefits, the vast implications for improvement in mental health, for both patients and carers, cannot be over-estimated.
11. There are case reports of neutralizing antibody limiting the effect of metreleptin. Would stakeholders expect that to be the case in a significant proportion of treated patients and what impact would be expected on outcomes such as HbA1c and triglycerides in the long term?	We don't have any reports of that adverse side effect from our patient population
12. For patients who discontinued metreleptin, would some long-term partial continued treatment effect in HbA1c, liver disease progression, hyperphagia, impaired physical appearance, and quality of life (QoL) benefits (for patients and carers) be reasonable to assume? If yes, by what mechanism? If this is thought likely, for how long a continued effect of metreleptin treatment on the above outcomes is clinically plausible? And how much?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
13. Is there a correlation between surrogate outcomes such as HbA1c and clinical outcomes such as cardiovascular and kidney diseases in people with LD and is this the	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation

same as seen in other diseases, for example, diabetes?	
Issue 5: Discontinuation rate of metreleptin treatment	
14. What discontinuation rate on metreleptin treatment is likely to be seen in UK clinical practice?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
15. Is a constant annual discontinuation rate of 1.50% for GL patients and 3.86% for PL patients from NIH study representative of what would happen in clinical practice? Alternatively is a declining rate of 8.93% in year 1 (which closely reflects the discontinuation observed in the first year of the NIH trial), and 5.63% in years 2-9 and 2.04% in years 10 onwards (representing the decline in discontinuation over time)more plausible?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
Issue 6: Baseline transition probabilities and pathway through organ sub-models	
16. Is it appropriate to assume that patients with diabetes or elevated triglyceride levels, due to lipodystrophy, will follow a similar course to patients with similar metabolic abnormalities but caused by different underlying diseases, and therefore patients with lipodystrophy will follow the same pathway through the organ sub-models, according to the same transition probabilities as patients with similar metabolic	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation

conditions but caused by different underlying disease states?	
17. Can the stakeholders provide feedback on the extent to which these input values and transition probability estimates are generalisable to patients with lipodystrophy? Are the populations used to estimate transition probabilities generalisable for UK clinical practice?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
18. Is it appropriate to use HbA1c or ALT/AST to adjust the transition probabilities and account for the reduction in risk of organ complications associated with metreleptin in sub-models?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
Issue 7: Metreleptin's continued treatment effect on HbA1c post-discontinuation	
19. (1st part of question 19) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
20. Is it appropriate to assume that, post-discontinuation of metreleptin treatment, the relative efficacy of metreleptin compared with supportive care would remain constant over the life time, and the change in HbA1c level will be the same in the metreleptin and supportive care groups?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation

21. Would a scenario in which only a proportion of patients would experience the 0.15% increase in HbA1c after the 1st cycle be possible?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
Issue 8: Metreleptin's continued treatment effect on liver complications post discontinuation	
19. (2nd part of question 19) Is it appropriate to assume that discontinuation of metreleptin had no impact on its effect on HbA1c level in the long term and in the four organ sub-models using HbA1c to determine transition probabilities?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation
Issue 9: Metreleptin's continued treatment effect on quality of life (utility differential) post-discontinuation and assumptions around additional utilities used in the model	
22. Is it appropriate to use utility values from the literature based on populations with disorders other than LD, on which the sub-models are based and apply them to LD populations at the same state in the model?	With regards to discontinuation of treatment, there have been similar fears communicated throughout the lipodystrophy community. As above, the following statements have been taken from the survey responses when asked 'What are your/(and/or) the patients' concerns if metreleptin treatment is withdrawn?' "Those who respond positively to the treatment will have their one defense against the relentless nature of the disease stripped away. I said it in the NICE meeting and I will say it again here; to a healthy person it is hard to understand, but the impact of hunger cannot be overstated. Financially, physically, mentally. Feeling full shouldn't have to feel like a revelation to anyone, especially not to those whose treatment is so heavily dependent on good diet. NICE want data on the hunger impact of Metreleptin and I say it's already there. Hunger is a roadblock to achieving the quantifiable results of hba1c, lipid profiles etc. Metreleptin is the only wrecking ball we have to

	get rid of that obstacle." "Withdrawal of Metreleptin treatment would be a tragedy for many patients who need it. Metreleptin is a lifesaving treatment for many - without leptin, my triglycerides would be through the roof and numerous organs would be full of fat, putting myself at extreme risk. And I am one of the lucky ones. There are other patients who, before Metreleptin treatment, were near death. Metreleptin has saved many lives, and it is critical that patients have access to this lifesaving treatment." "Metreleptin should be easily available to all patients in a globe as that is the only treatment available currently" [sic] "It would be devastating and my general health would deteriorate, I would be very frightened about my future without Leptin, I believe it has delayed crisis outcomes." "I feel I would have more premature health complications and a less likelihood of surviving these complications if I was not on Leptin" "That I will revert to being severely resistant to Insulin with all the issues that entails. It will have huge consequences on my physical and mental health as I depend on Leptin to keep me on a positive level and excellent diabetic control." "I am terrified of loosing access and going back to constant hunger and being sick 3 out of ever 4 weeks. I will not be able to maintain my employment."

	"The FPLD 2 and complications would resurface. Medication would be required for my diabetes. The ischemic heart disease would progress further, particularly as the combination of ezetimbe, atorvastatin, bezafibrate and restricted diet was not enough to keep my diabetes and mixed hyperlidaemia under control, which in turn would result in my ischemic heart disease progressing further and an early death" "Absolutely terrified, as the heart disease will worsen, as will the diabetes, hunger, mixed hyperlipidaemia. This worry is constantly on our minds" "My life will become majorly harder than it already is. My life will be shortened. My mental health will further deteriorate" "I'm terrified of going back to a life without leptin. The hunger is all consuming and incredibly painful"
23. Is it appropriate to assume additional differential in utility (measure of QoL) between patients receiving metreleptin and standard of care (0.12 based on the DCE study) to account for changes in quality of life not captured by the health states in the sub-models? Similarly should there be a disutility due to the burden of caring in the models? If yes, is it appropriate to assume that some of these additional utilitities would be maintained post-discontinuation (over the patient's lifetime) and why?	Lipodystrophy UK is unable to contribute to specific clinical or economic questions in relation to this consultation

Issue 10: Number of carers used in the model	
24. On average, how many carers are needed for the caring of a person with LD and will this change throughout their lifetime e.g. more or fewer as people reach adulthood?	The impact of caring for a child with lipodystrophy has far reaching implications for the entire family unit and can be all consuming, especially for example, if a child experiences severe organ abnormalities. This is a particular problem for families of children with generalised lipodystrophy. Organ damage and associated complications can have a lifelong impact on those affected (both for the patient and the carer), with the need for continuing care.
Other considerations:	
25. Population indicated for metreleptin include children, are there any additional considerations required?	Not that we are aware

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Metreleptin for treating lipodystrophy: re-submission [ID861]

ADDENDUM: Critique of the company's response to Technical Engagement

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Introduction

This addendum contains the following:

1) ERG critique of the company response to the issues raised in the technical report.[1]
2) The ERG critique of the company's updated cost effectiveness results, as presented in the response to the technical report.[1]
3) Exploratory and scenario analysis undertaken by the ERG.
4) ERG conclusions regarding the cost effectiveness analysis.

1. Company's response to technical engagement

Issue 1 The clinical use of metreleptin in consideration of its current marketing authorisation/ Population that would be eligible for treatment

Question 1

The company appear to have narrowed the index population, i.e. as to be applied in UK clinical practice, by including the stipulation of minimum levels of HbA1c and fasting triglycerides. However, it is also stated that these criteria would be relaxed under some conditions e.g. *"…extreme hyperphagia and/or severe side effects from other glucose lowering medications, or other serious complications of inadequate metabolic control such as progressive liver disease"*. However, it is unclear as to the size of the population given lack of information as to the number of patients who would actually fulfil these criteria including the exceptions. It is also difficult to understand why these specific levels were chosen given that they are not the same as the PL subgroup in CS, i.e. baseline HbA1c>7.5% and/or fasting triglycerides >5.0 mmol/L instead of HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L. Given that the HbA1c threshold is higher, but the triglyceride threshold lower and the lack of information on the number and precise nature of the exceptions, it is difficult to predict the consequences on the effectiveness of metreleptin. This therefore has implications for the applicability of the various data sources to UK clinical practice (See Issues 2 and 3).

The stopping rule was already included in the company submission and therefore the ERG have nothing further to add on this point.

Questions 2 and 3

The ERG has nothing further to add.

Issue 2 Representativeness of studies used to inform clinical effectiveness of metreleptin

Question 4

The ERG would like to highlight the discrepancy between the PL subgroup and the index population as defined in Issue 1, the implications of which are uncertain. In relation to the applicability of the studies used in the ITC, the ERG would like to restate the suggestion in the ERG report that the evidence from the Addenbrooke's EAP is likely to be more applicable to UK clinical practice, assuming no change in the eligibility criteria as actually applied in clinical practice (See Questions 5, 6 and 8 for further discussion).[2]

Question 5

The ERG concurs with the company regarding the mistake in the Addenbrooke's EAP GL triglyceride data, corrected by the ERG post-FAC.

The ERG would also agree that the size of the treatment effect is liable to vary depending on whether absolute or percentage change is considered. It is also plausible that part of the explanation of the lower absolute change in triglycerides might be the lower baseline values in the EAP patients (see Table 1 in the company response). The ERG would also agree with the assertion that the ITC might produce a treatment

effect that is more applicable to clinical practice that an unadjusted difference between any metreleptin study and the Natural History study. However, as described for Issue 1, there remains some doubt as to the precise eligibility criteria that would apply in clinical practice and the only experience of such practice so far is the EAP. Therefore, the ERG would like to restate the suggestion in the ERG report that there might be some value in comparing the results of the ITC using the Addenbrooke's EAP data with those using the NIH follow-up study.[2]

Question 6

In relation to the applicability of the EAP, the company argue that the severity of patients eligible in the past was lower than would be the case today. This does therefore potentially undermine the applicability of the EAP data to UK clinical practice. However, it is unclear what the difference in the discrepancy between the past and today would be between the EAP and the NIH studies 991265/20010769. Indeed, in a similar way as for the EAP, the NIH studies 991265/20010769 data might also be less applicable. It is also important to note that for both datasets, PL subgroup data are available and there is no evidence that the eligibility criteria for GL patents will change. Therefore, given that the implications of the eligibility criteria for PL patients suggested by the company are unclear (see Issue 1) and that the EAP data would still have the advantage of being from UK treated patients, the ERG would still argue that it might still be more applicable than the NIH studies 991265/20010769 data.

Issue 3 The treatment effect of metreleptin compared with supportive care/the indirect treatment comparison

Question 7

The company have reiterated the assertion that the inclusion of the additional covariates HbA1c or triglyceride level was not feasible. However, they go on to say that their inclusion in a sensitivity analysis caused 'and avoidable loss of precision.' The ERG would therefore question the correspondence between lack of feasibility and loss of precision and would argue, as in the ERG report, for a full report of the results of that sensitivity analysis.[2]

Question 8

In relation to the relative applicability of the EAP and the NIH studies 991265/200110769, the company claim that in terms of HbaA1c and triglyceride levels the patients in the former are less severe. The ERG would concur that, as can be observed in Table 1 of the company response, the values for PL patients are lower in the EAP dataset. On the other hand, most of the values for GL patients are higher in the EAP dataset. However, the applicability of any dataset will depend largely on the degree of concordance between the type of patients in the dataset and those treated in clinical practice. Notwithstanding the claim by the company of the difference in patient type between the past and the present, the implications of the eligibility criteria for the type of PL patient treated is uncertain (see Issue 1). In particular, the implication of there being exceptions to the need to fulfil minimum levels of HbA1c and triglycerides is that there must be patients with values of HbA1c and triglycerides that are lower and thus with less severe disease at least according to those criteria. Therefore, given that the only experience of UK clinical practice so far is the EAP, which might have included such patients, the EAP data might still be considered more applicable than the NIH studies 991265/200110769.

Issue 4 Lack of evidence on long-term treatment effect of metreleptin; and metabolic measures such as HbA1c, triglycerides and hepatic enzymes as surrogate for long-term hard clinical outcomes in people with LD

Questions 9 to 11

No new evidence was presented in the company response. Therefore, the ERG would like to restate that there is a lack of long-term evidence for metreleptin (for surrogate outcomes such as HbA1c beyond 36 months and only from the EAP) and no evidence in the index population, which is LD, for the relationship between surrogate outcomes and progression of multi-organ damage.

Question 12

HbA1c

The company was still not able to provide evidence on the length of time and level of treatment benefits that would likely be observed after discontinuation from metreleptin therapy. They argue that HbA1c is a marker of glucose control, with the lack of glucose control being the cause of diabetes related complications, which develop over many years at a rate and extent that is related to the adequacy of glucose control. Therefore, it would be clinically implausible to assume that the rate of loss of benefit in the avoidance of complications would be instantaneous and revert to standard of care (SoC) rates following metreleptin discontinuation as in the ERG base-case.

First the ERG would like to note that the way HbA1c is modelled means that the full efficacy of metreleptin is assumed in the year of discontinuation. This means that on average, patients receive an additional 6 months of full metreleptin efficacy or, assuming that efficacy would steadily wane towards SoC risk of complications, 1-year of waning post-discontinuation efficacy. Therefore, the comments by the company throughout their response to technical engagement that the reversal is instantaneous in the model is incorrect. The company have provided no evidence that suggests a longer period of post-discontinuation efficacy would be justified and certainly no evidence for their base-case assumption which results in an average post-discontinuation efficacy of over 20 years full efficacy plus 14 years waning efficacy in GL patients and over 20 years full efficacy and 6 years waning in PL patients (see Table 5.8 in the ERG report).[2]

Additionally, the company state "elevated levels of HbA1c are used as measure of glucose control over time and reflect levels over several months". Therefore, while it may take time for HbA1c levels to rise, glucose control is in fact lost at the time of discontinuation and will begin to have consequences on risk.

Furthermore, if there is indeed a lag assumed between glycaemic control (marked by HbA1c) and impact on the risk of complications, this would presumably also apply at the beginning of treatment, where patients would still be at higher risk due to poor previous glycaemic control than the level of risk suggested by their drop in HbA1c. This is not modelled. Therefore, the ERG would argue that their modelling of HbA1c accounts for the time on treatment (and therefore time over which patients have superior glycaemic control) and the associated lowering of risk of diabetes complications. An additional 6 months full efficacy or 1-year waning efficacy is also given to allow for the possibility of a short period of extended efficacy after treatment. However, the company have provided no evidence for post-discontinuation efficacy over this period or any more extended period.

Lastly, the ERG would like to reiterate from the ERG report that their modelling of the reversal of the HbA1c treatment effect upon discontinuation was based on TA315, from where the assumed 0.15% annual increase in HbA1c was taken.[2, 3] TA315 also modelled the full reduction in HbA1c due to treatment upon treatment initiation and then applied an annual increase in HbA1c across all patients. However, upon treatment discontinuation the company modelled a reversal in the treatment related reduction in HbA1c, as they did not have evidence of continued benefit after discontinuation.[3]

The ERG does note the company's comment that the ERG's reversal of HbA1c reverses the treatment effect on top of the accumulated drift in HbA1c over the treatment period. The company argue that it is implausible that patients would return directly to the equivalent HbA1c of the standard of care arm rather than return to their baseline level of HbA1c. The company conducted a scenario whereby upon treatment discontinuation, HbA1c marker level returns to baseline (not including a 0.15% annual drift) at the point of discontinuation (rather than above the baseline level as implemented by the ERG's amendment). The ERG consider that this assumption could be plausible and include it in their updated base-case. Scenarios will be run around this assumption to reflect the uncertainty.

Liver

The ERG note the company's argument that in a patient discontinuing metreleptin therapy, it is not clinically plausible that the physical level of liver damage would instantly reverse to be that of a patient in the SoC arm and that it would take several years to return to a baseline level of risk for progressive liver disease. Again, the ERG note that their modelling of liver risk assumes an average of 6 months full efficacy before transition probabilities in the liver model are equal to those in the SoC arm or 1-year of waning efficacy. It is not true that risk immediately reverses to that of SoC patients.

The company refer to expert opinion that residual liver benefits will be retained but do not reference or further details are available for the ERG to verify.

Lastly, the company's statement that it would take several years to return to a baseline level of risk for progressive liver disease does not match their modelling of lifetime continued efficacy post metreleptin discontinuation or their scenarios of 5 or 9 years discontinuation (which are applied on top of the period of post-discontinuation efficacy already applied within the model structure). The ERG remains uncertain on the true period and level of post-discontinuation efficacy when it comes to the liver. Given the statement that patients would return to their baseline risk after several years, the ERG use the company's scenario of 1-year post-discontinuation (which is applied on top of the ERG's 6 months full or 1-year waning efficacy) in their updated base-case, to reflect the possibility that it takes several years to return to baseline risk. Scenarios will be run around this assumption.

Quality of life

Here the company present similar arguments that UK clinicians agree that it is clinically implausible to assume that treatment benefits associated with metreleptin would be reversed immediately upon discontinuation. The company state that some symptoms, such as hyperphagia, or markers, such as HbA1c, will return in a short period. However, given that lipodystrophy is a chronic progressive disease, the company believes it is reasonable to assume that a patient treated with metreleptin post-discontinuation will have slower glycaemic-related tissue damage and accumulation of ectopic fat in the liver compared to a

patient who has never been treated with metreleptin, and will therefore maintain residual quality of life (QoL) benefit post-discontinuation until death.

The ERG notes here the importance of remembering what is captured in the QoL treatment effect and what is captured in the sub-models. When patients transition to more progressed states in the organ sub-models, they receive the relevant decrement in utility, separate to the utility differential observed between patients on mexiletine and SoC. Therefore, decisions about post-discontinuation benefits in QoL are separate to post-discontinuation benefits in terms of reduced risk of organ complications in the sub-models.

The utility differential between metreleptin and SoC was intended to capture symptoms of lipodystrophy not captured in the organ models such as hyperphagia, impaired physical appearance, disruption to female reproductive functioning and inability to perform work/schoolwork. The company state that symptoms such as hyperphagia will return in a short period after discontinuation. Presumably, given that utility decrements included in the organ sub-models will already have captured the impact of organ complications on ability to work and perform usual activities, the ability to perform work/schoolwork element of the treatment differential is intended to capture the impact of LD specific symptoms such as hyperphagia on ability to work. Therefore, it would be expected that if symptoms such as hyperphagia return quickly, so does the associated inability to work. Given that together these two symptoms account for approximately 80% of the treatment differential as calculated by the ERG from the company's rescaled DCE decrements for the relevant LD symptoms (see Table 1.1), the ERG does not consider there to be a strong argument for long term post-discontinuation treatment differential for patients, or the associated benefit to carers. Especially given the consideration that if hyperphagia returns, potentially so does impaired physical appearance.

Table 1.1: Rescaled DCE decrements and prevalence of symptoms and complications

Symptom/ complication	Rescaled decrement	Prevalence				Treatment differential*
		GL Pre-treatment	PL Pre-treatment	GL Post-treatment	PL Post-treatment	
inability to perform work/ schoolwork	0.167	57.4%	20.5%	11.8%	9.1%	0.044
hyperphagia	0.071	82.3%	71.9%	11.3%	9.4%	0.047
PCOS	0.026	47.7%	77.4%	27.3%	64.5%	0.004
impaired physical appearance	0.056	82.4%	68.2%	29.4%	40.9%	0.022
	Total treatment differential					0.1167

* calculated assuming 43.5% GL patients and 56.5% PL patients as per baseline model characteristics
Based on ERG Report Table 5.10.[2]
GL = generalised lipodystrophy; PCOS = polycystic ovary syndrome; PL = partial lipodystrophy

Again, the ERG note that the way that QoL for patients and carers is modelled in their base-case means that the risks of complications and the treatment differential remain those related to patients treated with metreleptin until the cycle after discontinuation, implying 6 months full efficacy post-discontinuation or 1-year waning efficacy. No evidence has been provided that justifies a period of efficacy beyond this.

Question 13

No further evidence on the correlation between surrogates and organ complications specifically in LD patients was presented beyond the consensus from the Delphi Panel clinical experts that HbA1c is a predictive factor in the development of kidney disease, retinopathy, neuropathy, and cardiovascular disease in lipodystrophy patients. There is also no evidence on whether the relationships between surrogates and clinical outcomes are the same as seen in other diseases such as diabetes and therefore these uncertainties remain. The company do add that clinical expert opinion has highlighted that the insulin resistance in lipodystrophy is more severe than in diabetes and is likely to lead to worse organ-related damage, independent of glucose levels however no further details were provided.

Issue 5 Discontinuation rate of metreleptin treatment

Questions 14 and 15

In response to the question of whether the declining annual rate of discontinuation from the NIH study, selected by the ERG in their base-case, could be more plausible the company accepted that this would be a plausible alternative to their preferred discontinuation rates. The company also acknowledged that the declining rates have previously been accepted by the NICE Committee at the Final Evaluation Document (FED) stage. The company's updated base-case includes the declining discontinuation rates in line with the ERG base-case. The ERG agrees with this choice.

Issue 6 Baseline transition probabilities and pathway through organ sub-models

Question 16

The company did not provide any new evidence in relation to this question, simply reiterating information from the CS that the Delphi Panel which included UK clinicians reached consensus that early-onset type 2 diabetes is the closest form of diabetes observed in lipodystrophy patients. The ERG would note that expert opinion that early-onset type 2 diabetes is the closest form of diabetes observed in lipodystrophy patients does not mean that the transition probabilities in the model closely reflect the disease trajectory of lipodystrophy patients. The ERG can make no further comment than that given in the ERG report as no more evidence is available.

Question 17

No new evidence has been presented showing that the input values and transition probability estimates in the model, obtained from non-lipodystrophy populations, are generalisable to lipodystrophy patients in UK clinical practice. These uncertainties remain.

Question 18

The ERG reiterates their preference for using data from the trial rather than an estimate of treatment effect from the Delphi panel. The ERG notes from updated ERG scenarios shown in Table 3.7, that the choice between using the AST/ALT data or the Delphi estimate to adjust liver transitions has a very small impact on the ICER, therefore this is not a big issue.

Issue 7 Metreleptin's continued treatment effect on HbA1c post-discontinuation

Question 19

See response to Question 12.

Question 20

The ERG agrees that the full relative efficacy for HbA1c is only maintained until the ceiling of 12% is reached in the SoC group, after which the relative efficacy wanes until it is null when patients in the metreleptin reach the ceiling. However, the time period over which relative efficacy is fully maintained and then wanes is very large in the company's base-case, as detailed in response to Question 12.

Question 21

The ERG agrees with the company that there is a lack of data to address this uncertainty, specifically pertaining to the proportion of patients within each arm that would be subject to a different rate of increase. The company conducted a scenario in which all patients experience a 0.1% annual HbA1c increase and a scenario in which all patients experience a 0.05% annual HbA1c increase.

Issue 8 Metreleptin's continued treatment effect on liver complications post discontinuation

This is a duplicate question. The company direct the reader to question 12 for more information about post-discontinuation treatment effect for liver complications.

Issue 9 Metreleptin's continued treatment effect on quality of life (utility differential) post-discontinuation and assumptions around additional utilities used in the model

Question 22

The ERG note that the impact on utility of the same symptoms or complications are not necessarily equal across conditions as the impact of the symptom/complication will depend also on the burden of the specific condition and whether there are other comorbidities which are having a simultaneous impact, which may not be entirely consistent across different conditions. Beyond this the ERG cannot make any further comment beyond the ERG Report as no additional evidence is presented in relation to this issue.

Question 23

The ERG agrees with the company that certain specific symptoms of lipodystrophy, including hyperphagia and body image issues are likely to have been missed in the organ model and therefore it is appropriate that these are captured. However, it is unclear to what extent issues such as the ability to work/perform schoolwork are already captured in the organ sub-model disutilities and therefore potentially double counted.

The ERG also agrees that it is appropriate to include carer disutilities within the model. However, the ERG notes that still no evidence has been presented on the continued efficacy of metreleptin on hyperphagia and continued impact on carers post-discontinuation. Please see the response to Question 12 for more details.

Issue 10 Number of carers used in the model

Question 24

The ERG reiterates their view that the mean should be included in the cost-effectiveness model to reflect the average numbers of carers and therefore will continue to use the mean number of carers of 1.67 in their base-case.

Tariff consistency issue

The ERG agrees that there should be consistency between tariffs and agrees with the use of the UK value set from Janssen and Szende rather than the England specific value set.[4] This change by the company increases the disutility due to caring back up to 0.0986 as per the company's base-case.

2. Company's updated cost effectiveness results

2.1 Company's updated deterministic results

The company provided updated cost-effectiveness results, with assumptions as per the company submission with the exception of:

- updated baseline age-dependent utilities based on UK Tariff
- updated ICER calculation as per question 12
- updated discontinuation rates as per question 15

With the exception of the amendments to age-dependent utilities (which was still carried out in a different way to in the ERG base-case) and the acceptance of the ERG preferred discontinuation rates, the company did not incorporate any of the other ERG preferred assumptions into their updated base-case. Therefore, the following assumptions from the ERG base-case were not incorporated or reflected in the company's updated results:

- The correction of the average number of carers in the model to 1.67 (reflecting the data mean) rather than 2 (which reflected the data median used in the company base-case)
- The use of the ALT/AST data to adjust transition probabilities in the liver model rather than the Delphi Panel data
- The reversal of HbA1c after discontinuation to remove the assumption of long-term post-discontinuation efficacy in relation to HbA1c
- The removal of the assumed lifetime post-discontinuation efficacy in the liver model
- The removal of the assumed lifetime maintenance of 50% of the QoL treatment differential and carer utility gain post-discontinuation from metreleptin

The company's updated deterministic results are shown in Table 2.1. The ICER for LD patients overall was £118,895 per QALY gained. As per previous base-cases, the ICER was lower for GL patients than for PL patients. Updated probabilistic results were not provided.

Table 2.1: Company's updated deterministic results

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL	[redacted]	[redacted]	£91,407
PL	[redacted]	[redacted]	£158,351
Overall	[redacted]	[redacted]	£118,895

*QALY weighting applied
Source: Company's response to technical engagement.[1]
GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PL = partial lipodystrophy; QALYs = quality adjusted life years.

2.2 Company scenario analyses

The results of the company scenarios for GL and PL patients overall are provided below in Table 2.2. For results per GL and PL subgroup, results can be found in the company's response to technical engagement.[1] The scenarios which had the largest impact on the ICER were assuming simultaneously that HbA1c was reversed to baseline level upon discontinuation in combination with the maintenance of liver benefits and 50% QoL benefits for patients and carers for only 1-year post discontinuation, which resulted in an ICER of £194,263. The elements of post-discontinuation benefits which have the largest impact on the ICER are the maintenance of 50% of QoL benefits for patients and carers, followed by liver benefits. This shows the importance of these assumptions in the model.

Table 2.2: Results of the company's scenario analyses

Scenario	Incremental costs	Incremental QALYs	ICER £/QALY
Updated Company BC	[redacted]	[redacted]	£118,895
Post discontinuation HbA1c			
Reversion of HbA1c to baseline level upon discontinuation	[redacted]	[redacted]	£119,997
Maintenance of liver benefits post discontinuation			
1-year post-discontinuation	[redacted]	[redacted]	£138,087
5 years post-discontinuation	[redacted]	[redacted]	£132,380
9 years post-discontinuation	[redacted]	[redacted]	£128,492
Maintenance of QoL benefits post discontinuation			
Maintenance of 50% QoL treatment and carer benefits for 1-year post-discontinuation	[redacted]	[redacted]	£180,575
Maintenance of 50% QoL treatment and carer benefits for 5 years post-discontinuation	[redacted]	[redacted]	£167,551
Maintenance of 50% QoL treatment and carer benefits for 9 years post-discontinuation	[redacted]	[redacted]	£157,755
Reversal of HbA1c to baseline level and maintenance of liver benefits and 50% QoL benefits for patients and carers post discontinuation			
1-year post-discontinuation	[redacted]	[redacted]	£194,263
5 years post-discontinuation	[redacted]	[redacted]	£175,917
9 years post-discontinuation	[redacted]	[redacted]	£163,130
HbA1c annual drift			
All patients 0.1% annual increase	[redacted]	[redacted]	£110,223
All patients 0.05% annual increase	[redacted]	[redacted]	£101,368
Source: Company response to technical engagement.[1]			

Scenario	Incremental costs	Incremental QALYs	ICER £/QALY
Updated Company BC	[redacted]	[redacted]	£118,895
BC = base-case; HbA1c = glycated haemoglobin; ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years; QoL = quality of life			

The company also provided results of an updated run of the ERG base-case with assumptions as per the ERG report, but with updated baseline age-dependent utilities based on UK Tariff. This resulted in an updated ERG base-case deterministic ICER of £224,744, instead of £241,531.[1]

3. Exploratory and scenario analyses undertaken by the ERG

The ERG made several changes to their base-case in response to the company's technical engagement response. The updated ERG base-case included:

- the company's updated scenario modelling of the HbAc1 reversal to baseline level (not including the drift observed over the treatment period) upon-discontinuation
- the company's updated baseline age-dependent utilities based on the UK Tariff (which increased the disutility due to caring back up to 0.0986 as per the company's base-case)
- An additional year of post-discontinuation efficacy in the liver model.

The ERG also made the following amendments to the company's updated base-case in line with the ERG's original base-case:

- The correction of the average number of carers in the model to 1.67 (reflecting the data mean) rather than 2 (which reflected the data median used in the company base-case)
- The use of the ALT/AST data to adjust transition probabilities in the liver model rather than the Delphi Panel data
- The removal of the assumed continued 50% of the QoL treatment differential and carer utility gain post-discontinuation from metreleptin (no additional years assumed beyond the 6 months full efficacy already modelled)

The ERG's updated base-case results are displayed in Table 3.1. Overall, across both subgroups, treatment with metreleptin costs an additional [redacted] for a QALY gain of [redacted] resulting in an ICER of £217,128. Incremental costs are higher in the GL subgroup, but this is outweighed by substantially higher incremental gains, resulting in a lower ICER of £185,088 in the GL subgroup compared to £252,765 in the PL subgroup.

Table 3.1: ERG base-case deterministic results (discounted)

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL	[redacted]	[redacted]	£185,088
PL	[redacted]	[redacted]	£252,765
Overall	[redacted]	[redacted]	£217,128

Based on the electronic model, updated from the company's response to technical engagement.[1]
GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PL = partial lipodystrophy; QALYs = quality adjusted life years.

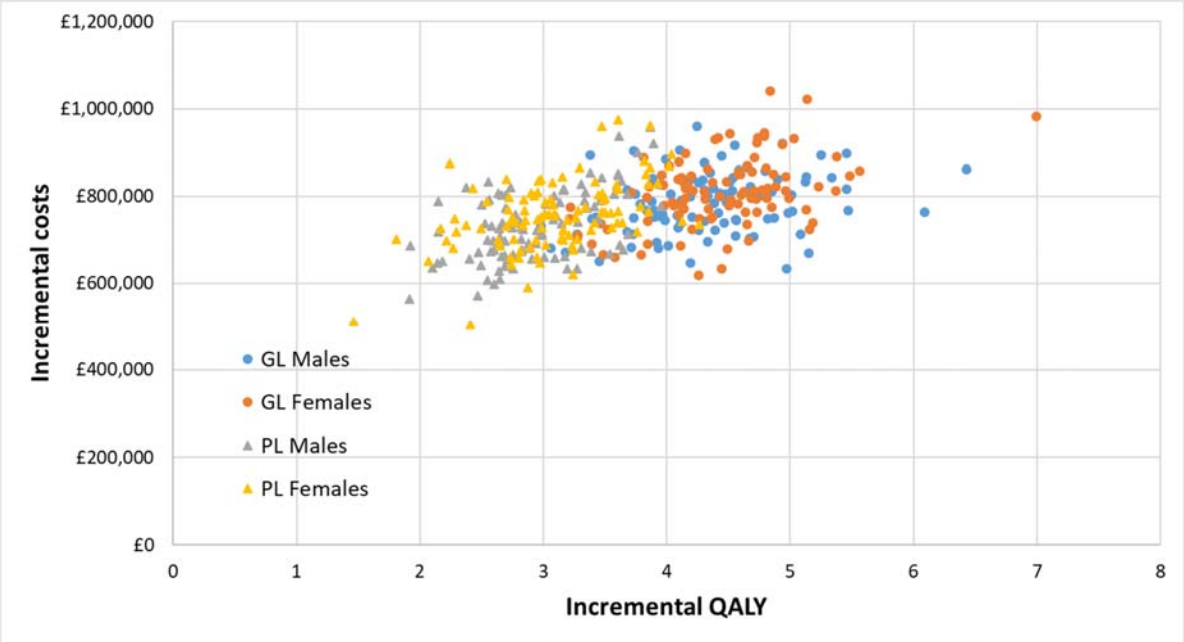
The ERG also ran a PSA on their updated base-case, with results shown in Table 3.2 below. Due to time constraints a reduced PSA of 100 cohorts of 100 patients had to be run. The probabilistic ICERs were well aligned to the deterministic ICERs, although more variation was seen for the PL subgroup. As can be seen GL patients tend to receive a larger QALY gain than PL patients at a slightly higher cost. Figure 3.2 displays a scatterplot of the PSA outcomes on the CE-plane. The cost effectiveness acceptability curve (CEAC) in Figure 3.2 shows that at a threshold of £100,000, the probability of metreleptin being cost effective is 0 for both subgroups. At a threshold of £200,000, the probability of being cost effective is 79% in GL patients, 5% in PL patients and 24% overall.

Table 3.2: ERG base-case probabilistic results (discounted)

Population	Incremental costs (£)	Incremental QALYs	ICER (£)
GL	[redacted]	[redacted]	£182,221
PL	[redacted]	[redacted]	£244,525
Overall	[redacted]	[redacted]	£211,906

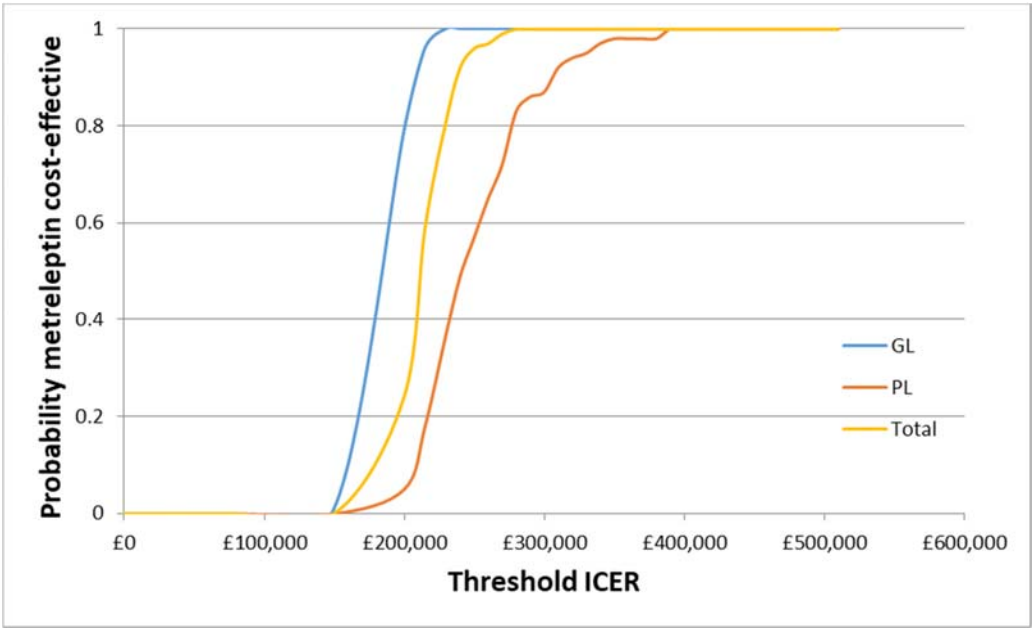
Based on the electronic model, updated from the company's response to technical engagement.[1]
GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PL = partial lipodystrophy; QALYs = quality adjusted life years.

Figure 3.1: ERG base-case cost-effectiveness plane



Based on the electronic model, updated from the company's response to technical engagement.[1]
GL = generalised lipodystrophy; PL = partial lipodystrophy; QALY = quality-adjusted life year.

Figure 3.2: ERG base-case CEAC



Based on the electronic model, updated from the company's response to technical engagement.[1]
GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PL = partial lipodystrophy.

3.1 Additional scenarios conducted by the ERG

Additional scenarios were run with a single cohort of 1000 patients using fixed seeded values. Some unexpected differences may be seen for scenarios which were equal to the ERG updated base-case, as this was run using 3000 patients using fixed seeds and therefore some variation may be due to variation between patients.

3.1.1 Scenario set 1: Post-discontinuation HbA1c

One of the remaining issues was how to model post-discontinuation HbA1c. The company base-case assumed that discontinuation had no impact on HbA1c, which continued drifting until it reached the ceiling of 12% resulting in long-term post-discontination efficacy as outlined in the ERG's response to Question 12. In the ERG original base-case, in the cycle after the discontinuation cycle, the reduction in HbA1c observed in the first cycle of treatment was added back onto the current HbA1c level to fully reverse the treatment effect. The company argued that patients who discontinued would not immediately have the risks associated with the SoC arm after and ran a scenario where, in the cycle after discontinuation, the baseline level of HbA1c, not accounting for drift over the treatment period was restored, so that patients who discontinued returned to their baseline level of risk. The EGR considered that this could be plausible and updated their base-case to this scenario. The company's base-case assumption that there was no impact of discontinuation on HbA1c was retained in their base-case. The results in Table 3.3 show that the assumption made here has a limited impact on the ICER. Assuming no impact on HbA1c upon discontinuation provides the lowest ICER of £216,890, while fully removing the HbA1c treatment effect in the cycle after

discontinuation provides an ICER approximately £6,000 higher at £222,836. This would suggest that this issue in itself is not of huge importance.

Table 3.3: ERG HbA1c post-discontinuation scenarios

	Incremental Costs (£)	Incremental QALYs	ICER (£)
Full reversal of HbA1c upon discontinuation (including drift) (ERG BC)	[redacted]	[redacted]	£222,836
Reversal of HbA1c to baseline level upon discontinuation (not including drift) (ERG updated BC)	[redacted]	[redacted]	£217,128
No reversal of HbA1c upon discontinuation (Company BC)	[redacted]	[redacted]	£216,890

Based on the electronic model, updated from the company's response to technical engagement.[1]
BC = base-case; HbA1c = glycated haemoglobin; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

3.1.2 Scenario set 2: Post-discontinuation benefits liver

Table 3.4 shows that the assumed length of time over which liver benefits are assumed post metreleptin discontinuation does not have a large impact on the ICER. Assuming lifetime post-discontinuation benefits as in the company model results in an ICER of £213,358, while assuming no additional years (beyond the 6 months full or 12 months waning post-discontinuation efficacy) results in an ICER approximately £7,000 higher at £220,366.

Table 3.4: ERG liver post-discontinuation benefit scenarios

	Incremental Costs (£)	Incremental QALYs	ICER (£)
No additional years (ERG original BC)	[redacted]	[redacted]	£220,366
1 additional year (ERG updated BC)	[redacted]	[redacted]	£217,128
5 additional years	[redacted]	[redacted]	£216,406
Lifetime (Company BC)	[redacted]	[redacted]	£213,358

Based on the electronic model, updated from the company's response to technical engagement.[1]
BC = base-case; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.

3.1.3 Scenario set 3: Post-discontinuation benefits QoL

As can be seen in Table 3.5, assumptions surrounding post-discontinuation QoL have a much larger impact on results. Assuming no additional years of benefits to patient or carer QoL post-discontinuation, as in the ERG base-case gives an ICER of £217,128, while assuming 50% of QoL benefits to patients and carers remain over the patient's lifetime reduces the ICER by approximately £55,000 to £162,105 per QALY gained. Therefore, the assumed impact of discontinuation on QoL is an important issue.

Table 3.5: ERG QoL post-discontinuation benefits scenarios

	Incremental Costs (£)	Incremental QALYs	ICER (£)
No additional years ERG BC	[redacted]	[redacted]	£217,128
1 additional year of 50% retained QoL benefits	[redacted]	[redacted]	£214,396
5 additional years of 50% retained QoL benefits	[redacted]	[redacted]	£198,723
Lifetime of 50% retained QoL benefits	[redacted]	[redacted]	£162,105
Based on the electronic model, updated from the company's response to technical engagement.[1] BC = base-case; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; QoL = quality of life.			

3.1.4 Scenario set 4: Post-discontinuation benefits HbA1c, liver and QoL

Applying the assumed post-discontinuation benefits from scenario sets 1-3 above in combination has a substantial impact on the ICER, mostly due to the importance of post-discontinuation QoL. As displayed in Table 3.6, assuming no additional years of post-discontinuation benefits beyond the 6 months full or 12 months waning already modelled results in an ICER of £223,713 per QALY gained. Assuming lifetime benefits, in combination with no reversal of HbA1c, results in an ICER of £143,340, a reduction of approximately £80,000.

Table 3.6: ERG post-discontinuation benefits HbA1c, liver and QoL combined scenarios

	Incremental Costs (£)	Incremental QALYs	ICER (£)
No additional years and full reversal of HbA1c (including drift)	[redacted]	[redacted]	£223,713
1 additional year and reversal of HbA1c to baseline (not including drift)	[redacted]	[redacted]	£214,396
5 additional years and reversal of HbA1c to baseline (not including drift)	[redacted]	[redacted]	£196,173
9 additional years and reversal of HbA1c to baseline (not including drift)	[redacted]	[redacted]	£182,696

	Incremental Costs (£)	Incremental QALYs	ICER (£)
Lifetime and no reversal of HbA1c	[redacted]	[redacted]	£143,340
Based on the electronic model, updated from the company's response to technical engagement.[1] BC = base-case; HbA1c = glycated haemoglobin; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.			

3.1.5 Scenario set 5: Number of carers per patient

Increasing the number of carers from 1.67 in the company base-case to 2 in the ERG base-case increases the ICER by approximately £12,000 per QALY gained, as seen in Table 3.7. This is quite a substantial increase, which would only be larger if longer post-discontinuation benefits for QoL were assumed. Therefore, this remains a fairly influential parameter.

Table 3.7: ERG number of patients per patient scenarios

	Incremental Costs (£)	Incremental QALYs	ICER (£)
2 carers (Company BC)	[redacted]	[redacted]	£205,452
1.67 carers (ERG BC)	[redacted]	[redacted]	£217,128
Based on the electronic model, updated from the company's response to technical engagement.[1] BC = base-case; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.			

3.1.6 Scenario set 6: Source of liver transitions

As shown by the results in Table 3.8 below, choice of which source to use to adjust the transitions in the liver model has little impact on results.

Table 3.8: ERG liver transition scenarios

	Incr. Costs (£)	Incr. QALYs	ICER (£)
Delphi Panel (Company BC)	[redacted]	[redacted]	£215,530
ALT/AST (ERG BC)	[redacted]	[redacted]	£217,128
Based on the electronic model, updated from the company's response to technical engagement.[1] ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = base-case; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years.			

4. ERG conclusions regarding the cost effectiveness analysis

The company submitted responses to the key issues raised in the Technical Report written by the NICE technical team as well as an updated company base-case and series of scenarios.

The focus of the technical engagement response by the company was on the extent of post-discontinuation benefits. The company provided a series of arguments, supported by expert opinion (no further details provided) for why the ERG's immediate removal of treatment benefits post-discontinuation in relation to HbA1c, liver and QoL was implausible. The ERG had several important points to note here about this issue generally. Firstly, the ERG did not immediately remove treatment benefit post-discontinuation. The way the ERG base-case is modelled means that the full efficacy of metreleptin is assumed in the year of discontinuation for HbA1c, liver and QoL. This means that on average, patients receive an additional 6 months of full metreleptin efficacy or, assuming that efficacy would steadily wane towards SoC risk of complications, 1-year of waning post-discontinuation efficacy. Therefore, the comments by the company throughout their response to the Technical Report that the reversal is instantaneous in the model is incorrect. Secondly, the ERG notes that no evidence of the efficacy of metreleptin post-discontinuation in relation to any of these aspects has been provided, beyond some references to clinical expert opinion for which no details are provided to enable the ERG to verify the comments.

The company argued that the ERG's reversal of HbA1c reverses the treatment effect on top of the accumulated drift in HbA1c over the treatment period. The company argued that it is implausible that patients would return directly to the equivalent HbA1c of the standard of care arm rather than return to their baseline level of HbA1c. The company conducted a scenario whereby upon treatment discontinuation, HbA1c marker level returns to baseline (not including a 0.15% annual drift) at the point of discontinuation (rather than above the baseline level as implemented by the ERG's amendment). The ERG consider that this assumption could be plausible and include it in their updated base-case. It should be noted that the company retained the assumption that discontinuation had no impact on HbA1c in their updated base-case.

The company also stated that it is not clinically plausible that the physical level of liver damage would instantly reverse to be that of a patient in the SoC arm and that it would take several years to return to a baseline level of risk for progressive liver disease. Given the uncertainty in relation to post-discontinuation efficacy, the ERG added an additional year of post-discontinuation efficacy in the liver model (on top of the 6 months full efficacy already assumed).

However, the company's arguments for continued benefits in relation to QoL were all focussed on the argument that a patient treated with metreleptin post-discontinuation will have slower glycaemic-related tissue damage and accumulation of ectopic fat in the liver compared to a patient who has never been treated with metreleptin, and will therefore maintain residual QoL benefit post-discontinuation until death. However, when patients transition to more progressed states in the organ sub-models, they receive the relevant decrement in utility, separate to the utility differential observed between patients on mexiletine and SoC. Therefore, decisions about post-discontinuation benefits in QoL are separate to post-discontinuation benefits in terms of reduced risk of organ complications in the sub-models. The utility differential between metreleptin and SoC was intended to capture symptoms of lipodystrophy not captured in the organ models such as hyperphagia, impaired physical appearance, disruption to female reproductive functioning and inability to perform work/schoolwork. The company state that symptoms such as hyperphagia will return in a short period after discontinuation. It would be expected that if symptoms such as hyperphagia return quickly, so would the associated inability to work. Given that together these two symptoms account for

approximately 80% of the treatment differential as calculated by the ERG from the company's rescaled DCE decrements for the relevant LD symptoms, the ERG does not consider there to be a strong argument for long term post-discontinuation treatment differential for patients, or the associated benefit to carers. Therefore, no change to the ERG base-case was made in relation to QoL post-discontinuation.

In relation to the remaining issues surrounding carer QoL, the company continued to argue that use of 2 carers per patient, as per the median of the data, rather than 1.67 patients per patient, as per the mean of the data, was more appropriate in the model base-case. The ERG still does not agree and retained the assumed 1.67 carers per patient in their updated base-case. The company did however present an amendment to the model whereby they solved the consistency issue relating to the use of different tariffs for age-adjusted general population utility values. The updated company base-case consistently used the UK tariff from Janssen and Szende, The ERG accepted this update in their updated base-case.

The company accepted the use of the ERG preferred time dependent discontinuation rates from the NIH studies in their updated base-case. However, the company and ERG still disagree on the source of values which should be used to adjust liver transition probabilities, with the company preferring the estimate from the Delphi panel and the ERG preferring to use the AST/ALT data from the trial.

The company presented an updated base-case, which most notably still assumed lifetime post-discontinuation efficacy, 2 carers per patient and liver transition adjustments based on the Delphi estimate. The updated overall ICER was £118,895 per QALY gained. The scenarios which had the largest impact on the ICER were assuming simultaneously that HbA1c was reversed to baseline level upon discontinuation in combination with the maintenance of liver benefits and 50% QoL benefits for patients and carers for only 1-year post discontinuation, which resulted in an ICER of £194,263. The elements of post-discontinuation benefits which have the largest impact on the ICER are the maintenance of 50% of QoL benefits for patients and carers, followed by liver benefits.

The ERG presented an updated ERG base-case, which was consistent with the original ERG base-case, with the exception that upon-discontinuation HbA1c returned to baseline level (not including drift over the treatment period), 1 additional year of liver benefit was assumed post-discontinuation and the company's updated tariff consistency for age-adjustment baseline utility values was accepted. This resulted in an overall deterministic base-case ICER of £217,128 per QALY gained. The probabilistic ICER was well aligned with the deterministic at £211,906 per QALY gained. The CEAC shows that at a threshold of £100,000, the probability of metreleptin being cost effective is 0 for both subgroups. At a threshold of £200,000, the probability of being cost effective is 79% in GL patients, 5% in PL patients and 24% overall. Similar to the company's scenario analyses, assuming lifetime post-discontinuation benefits simultaneously for liver and QoL while assuming no impact of discontinuation for HbA1c had the largest impact on results with an ICER of £143,340. QoL post-discontinuation benefit assumptions had by far the largest impact of the three elements on results. The model also remains sensitive to the assumed number of carers per patient. Other assumptions have a smaller impact on results.

References

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[3] National Institute for Health and Care Excellence. *TA315: canagliflozin in combination therapy for treating type 2 diabetes [Internet]*: NICE, 2014 [accessed 10.7.20]. 59p. Available from: www.nice.org.uk/guidance/ta315

[4] Janssen MF, Szende A, Cabases J, Ramos-Goñi JM, Vilagut G, König HH. Population norms for the EQ-5D-3L: a cross-country analysis of population surveys for 20 countries. *Eur J Health Econ* 2016;20(2):205-216.

Amryt Pharmaceuticals DAC
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4th January, 2021

Dear Jo,

Further to the most recent revised PAS approved by PASLU on 25th November 2020, the company has re-run the company's preferred base case (aligned to that submitted to the technical report consultation) using the revised PAS [redacted] and the results are presented below:

Population	Incremental costs	Incremental QALYs	ICER
Generalised lipodystrophy	[redacted]	[redacted]	£46,000
Partial lipodystrophy	[redacted]	[redacted]	£81,584
Overall	[redacted]	[redacted]	£60,611

Abbreviations: ICER, Incremental cost-effectiveness ratio; QALYs, Quality-adjusted life years

Text highlighted in blue and underlined is commercial-in-confidence information.

These analyses are based on the company's model as per that submitted to NICE at the technical report consultation stage using 3000 patients and one cohort.

Kind Regards

Fleur Taylor

General Manager, UK Amryt Pharma