31 May 2018
EMA/435156/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Myalepta

International non-proprietary name: metreleptin

Procedure No. EMEA/H/C/004218/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AGL	Acquired generalised lipodystrophy
ALCL	Anaplastic large-cell lymphoma
ALT	Alanine aminotransferase
APC	acid precipitation/clarification
APL	Acquired partial lipodystrophy
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve or analytical ultracentrifugation
BID	Twice daily
BLA	Biologics License Application
BMI	Body mass index
BWFI	Bacteriostatic water for injection
C3	Complement 3
CCI	container closure integrity
CD	circular dichroism
CFAS	Controlled Concomitant Medication Full Analysis Set
CFU	colony forming unit
CGL	Congenital generalised lipodystrophy
C_{max}	Peak serum concentration
CQA	critical quality attribute
CV	Coefficient of variation or column volume
ECL	Electrochemiluminescence
EU	European Union
DP	drug product
DR	diaretentate
ELISA	enzyme-linked immunosorbent assay
EOP	end of production
EU	Endotoxin units
FAS	Full Analysis Set
FDA	Food and Drug Administration

FMEA	Failure Mode and Effects Analysis
FPL	Familial partial lipodystrophy
FSE	full-scale engineering
FSG	Focal segmental glomerulosclerosis
FTIR	Fourier transform infrared spectroscopy
GL	Generalised lipodystrophy
HbA1c	Glycosylated haemoglobin-specific A1c fraction
HCP	host cell proteins
HDL-C	High-density lipoprotein cholesterol
HIC	hydrophobic interaction chromatography
HPLC	high performance liquid chromatography
HRP	horseradish peroxidase
HSL	N-β-ketocaproyl-DL-homoserine lactone
IBs	inclusion bodies
ICSR	Individual Case Safety Reports
IND	Investigational New Drug
IPC	in-process control
IV	Intravenous
kbp	kilo base pair
LAL	limulus amoebocyte lysate
LC/MS	liquid chromatography/mass spectrometry
LD	Lipodystrophy
LDL-C	Low-density lipoprotein-cholesterol
LOCF	Last observation carried forward
LOD	limit of detection
LOQ	limit of quantitation
LT	less than
MedDRA	Medical Dictionary for Regulatory Activities
MetSO	methionine sulphoxide
MCB	master cell bank
MPGN	Membranoproliferative glomerulonephritis
MRD	minimum required dilution
MS	mass spectrometry
NA	not applicable

NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NIH	National Institutes of Health
NLT	not less than
NMT	not more than
NWP	normalised water permeability
OD	optical density
OOS	out of specification
PACMP	post approval change management protocol
PK	Pharmacokinetics
PL	Partial lipodystrophy
PTCL	Peripheral T-cell lymphoma
PV	process validation
QA	quality attribute
QC	quality control
QD	Once daily
qPCR	quantitative polymerase chain reaction
RIA	Radioimmunoassay
RO	reverse osmosis
RP-HPLC	reversed-phase high performance liquid chromatography
RPN	risk priority number
RRT	relative retention time
RS	Reference Standard
RTS	Resolution Test Solution
SAE	Serious adverse event
SC	Subcutaneous
SMQ	Standard MedDRA Queries
S/N	signal/noise
SOC	System organ class
SOP	standard operating procedure
SmPC	Summary of Product Characteristics
SWFI	Sterile water for injection
TEAE	Treatment-emergent adverse event
THY	thioglycollate

T_{max}	Time to peak serum concentration
TOC	total organic carbon
TSA	tryptone soya agar
TSB	tryptone soya broth
TMB	tetramethyl benzidine
TSE	transmissible spongiform encephalopathy
UF/DF	ultrafiltration/diafiltration
ULN	Upper limit of normal
UV	ultraviolet
WCB	working cell bank
WC-CCP	well-controlled critical process parameter
WFI	water for injections

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Aegerion Pharmaceuticals Limited submitted on 21 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Myalepta, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2015.

Myalepta was designated as an orphan medicinal product EU/3/12/1022 in the following condition: Treatment of Familial Partial Lipodystrophy, EU/3/12/1023 in the following condition: Treatment of Barraquer-Simons syndrome, EU/3/12/1024 in the following condition: Treatment of Lawrence syndrome and EU/3/12/1025 in the following condition: Treatment of Berardinelli-Seip syndrome, all on 17 July 2012.

The orphan designations were transferred from Aegerion Pharmaceuticals Limited to Aegerion Pharmaceuticals B.V. during the procedure on 30 November 2017.

The applicant was changed from Aegerion Pharmaceuticals Limited to Aegerion Pharmaceuticals B.V. at the time of submission of response to the Day 180 LoOI.

The applicant applied for the following indication:

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

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

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designations of Myalepta as an orphan medicinal product in the approved indications. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that metreleptin was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0314/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0314/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indications.

Applicant's request for consideration

Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance metreleptin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 20 November 2014. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bart Van der Schueren Co-Rapporteur: Agnes Gyurasics

The application was received by the EMA on	21 December 2016
The procedure started on	19 January 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 April 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 April 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	18 May 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 October 2017
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: - GCP inspections of one investigator site and the sponsor site located in the United States between 08/05/2017 to 12/05/2017 and 15/05/2017 to 19/05/2017 respectively. The outcome of the inspection carried out was issued on:	30 June 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 November 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2017
The CHMP agreed on a list of outstanding issues in writing and in an oral explanation to be sent to the applicant on	14 December 2017
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 January 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	8 February 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	21 February 2018
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	22 February 2018
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	27 April 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	18 May 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Myalepta on	31 May 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Lipodystrophy (LD) syndromes are clinically heterogeneous inherited or acquired ultra-rare disorders characterised by selective but variable loss of adipose tissue, primarily subcutaneous fat (Garg, 2004 N Engl J Med 350(12): 1220-1234; Chan et.al, 2010, Endocr Pract 16(2): 310-323). The disease is associated with increased morbidity and mortality, as well as impaired quality of life.

The loss of adipose tissue in patients with LD can range from partial to more generalised, and some patients have concomitant accumulation of excess adipose tissue centrally. Underlying this loss of adipose tissue, are very low levels of the hormone leptin which closely correlate with the amount of fat mass present (Considine et.al, 1996, N Engl J Med 334(5): 292-295).

The lack of normal depots for storage of ingested fats results in hypertriglyceridaemia, which is often severe and predisposing patients to serious conditions such as acute pancreatitis, which can be life-threatening. Elevated triglyceride levels are also a known risk factor for cardiovascular disease. In addition, deposition of fat occurs in ectopic locations such as liver, heart, and muscle, leading to extreme insulin resistance and often to diabetes that is difficult to control, even with high doses of insulin.

2.1.2. Epidemiology

Although data are limited, the available data on prevalence for generalised lipodystrophy (GL; combined congenital and acquired) is slightly under 0.01 to <0.15 in 10,000 and the prevalence for partial lipodystrophy (PL; combined familial and acquired) is approximately 0.02 to <0.3 in 10,000.

Despite the limited data in the applied indication for metreleptin in PL which includes only these patients with more severe metabolic abnormalities, prevalence of this PL subgroup is likely to be <0.03 in 10,000.

2.1.3. Biologic features, aetiology and pathogenesis

Because of the loss of adipose tissue, levels of the adipocyte-secreted hormone leptin in patients with LD are very low (Haque et.al, 2002, J Clin Endocrinol Metab 87(5): 2395). Leptin is a naturally occurring, adipocyte-derived hormone and an important regulator of energy homoeostasis, fat and glucose metabolism, reproductive capacity, and other diverse physiological functions (Friedman et.al, 1998, Nature 395(6704):763-70; Zhang et.al, 1994, Nature 372(6505): 425-32.). The leptin deficiency observed in patients with LD results in a significant reduction in the ability to regulate hunger and energy, as well as glucose and fat metabolism.

Lipodystrophy syndromes are classified by aetiology, i.e., genetic or acquired, and by distribution of adipose tissue deficiency, i.e., generalised (occurring in a diffuse fashion) or partial (restricted to regional anatomical adipose depots), leading to 4 broad categories: congenital generalised lipodystrophy (CGL also known as *Berardinelli-Seip syndrome*), acquired generalised lipodystrophy (AGL, also known as *Lawrence syndrome*), familial partial lipodystrophy (FPL) and acquired partial lipodystrophy (APL also known as *Barraquer-Simons syndrome*) (Handelsman et.al, 2013, Endocr Pract 19(1): 107-116).

While there can be considerable heterogeneity in the degree of morbidity between patients with GL versus PL, the types of signs and metabolic abnormalities resulting from the partial to near complete loss of subcutaneous fat resulting in leptin deficiency are very similar.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Lipodystrophy is often associated with severe metabolic abnormalities, including hypertriglyceridaemia, insulin resistance, and/or diabetes, that can result in life-threatening co-morbidities such as acute pancreatitis, steatohepatitis, and/or accelerated atherosclerosis and mortality (Garg, 2004; Chan, 2010).

Overall, complications associated with both acquired and congenital/familial forms of GL and PL can be quite severe, requiring aggressive treatment and management over the lifetime of the patient.

The severe metabolic abnormalities associated with GL occur at a young age and may result in premature diabetic nephropathy, retinopathy, cardiomyopathy, recurrent attacks of acute pancreatitis, hepatomegaly, and organ failure (Garg, 2011, J Clin Endocrinol Metab 96(11): 3313-3325; Handelsman et.al, 2013, Endocr Pract 19(1): 107-116); Lima et.al, 2016, Diabetol Metab Syndr 8: 23.).

Chronic renal disease and membranoproliferative glomerulonephritis (MPGN) can occur due to longstanding, sub-optimally controlled diabetes. A high incidence of proteinuric nephropathies (e.g., MPGN and focal segmental glomerulosclerosis [FSG] as well as diabetic nephropathy) has been reported in patients with GL (Javor et.al, 2004, J Clin Endocrinol Metab 89(7): 3199-3207). AGL is also associated with a higher frequency of MPGN (Garg, 2004, N Engl J Med 350(12): 1220-1234).

Similarly, cardiovascular complications also occur with increased prevalence and earlier onset in patients with FPL (Hegele, 2001, Circulation 103(18): 2225-2229; Garg, 2000, J Clin Endocrinol Metab 85(5): 1776-1782).

Female patients with LD may develop alterations in their neuroendocrine functions resulting in hirsutism, enlarged polycystic ovaries, hyperandrogenism, irregular menstrual periods, or amenorrhoea (Musso et.al, 2005, Metabolism 54(2): 255-263). Leptin is one of the signals controlling sexual maturation, as LD patients have been shown to have delayed puberty and hypogonadotrophic hypogonadism (Oral et.al, 2002, J Clin Endocrinol Metab 87(7): 3110-3117; Mantzoros et. al, 1997, J Clin Endocrinol Metab 82(4): 1066-1070).

Patients with acquired forms of GL and PL have additional complications, due to the association with autoimmune disorders (such as juvenile dermatomyositis as well as systemic lupus erythematosus), themselves implicated in part to the development of the disease (Capeau et. al, 2006. Future Lipidology 1(5): 593-604).

Finally, the psychosocial impact of lipodystrophy is another significant comorbid factor: patients often experience psychological distress caused by changes in physical appearance from lipodystrophy and often resort to corrective measures including plastic surgery, e.g., muscle tissue transfer or autologous fat grafts, as well as dermal fillers (Brown et. al, 2016, J Clin Endocrinol Metab: jc20162466; Misra et.al, 2003, Medicine [Baltimore] 82(2): 129-146).

The only true diagnostic determination of the subtype among the 4 categories of LD is an identified genetic mutation. Without that, the subtype is determined by age of onset (generally earlier in generalised vs partial; generally earlier in congenital/familial vs acquired), patient presentation (more evenly distributed fat loss in generalised vs partial), and awareness of concomitant variables (predilection to autoimmune diseases in acquired vs congenital/familial).

2.1.5. Management

For patients with LD and associated diabetes and/or hypertriglyceridaemia, current available therapies include diet modification (low calorie, low fat, and low carbohydrate) and pharmacologic intervention with oral anti-hyperglycaemic agents, insulin, glucagon-like peptide 1 agonists, and/or lipid-lowering agents.

Current therapeutic options are thus limited and do not address the underlying cause of the disease, i.e., the lack of adipose tissue and resulting leptin deficiency.

Patients with milder metabolic abnormalities may be effectively treated with such therapies at the start of the disease process. However, the disease is progressive and those with more severe abnormalities often do not respond to these treatments due to the profound nature of their underlying abnormalities, especially when insulin resistance is severe and/or triglycerides are significantly elevated.

About the product

Metreleptin is a recombinant human leptin analogue. It is a 147 amino acid, polypeptide with one disulphide bond between Cys 97 and Cys 147 and differs from native human leptin by the addition of a methionine residue at its amino terminus.

Metreleptin exerts its function by binding to and activating the human leptin receptor (ObR), which belongs to the Class I cytokine family of receptors that signals through the JAK/STAT transduction pathway.

Leptin acts via multiple mechanisms to decrease triglyceride and other lipid intermediates in lipodystrophy patients, reducing their accumulation in tissues such as liver and muscle, and ameliorating severe insulin resistance, thereby improving hyperglycaemia and hypertriglyceridaemia (Petersen et.al, 2002, J Clin Invest 109(10): 1345-1350; Javor et.al, 2005, Hepatology 41(4): 753-760 ; Park et.al, 2007, Metabolism 56(4): 508-516 ; Chong et.al, 2010, Diabetologia 53(1): 27-35; Oral et.al, 2002, J Clin Endocrinol Metab 87(7): 3110-3117). Recent research has suggested that leptin may also inhibit pro-protein convertase subtilisin/kexin type 9 (PCSK9) (Vatier et.al, 2016, Diabetes Obes Metab 18(7): 693-7; Levenson et.al, 2016, Endocrinology 157(4): 1421-1429).

The claimed indication for Myalepta was as replacement therapy adjunctive to diet to treat the complications of leptin deficiency:

- in patients with congenital or acquired generalised lipodystrophy (LD), in adults and children 2 years of age and above;
- in patients with familial or acquired partial LD, characterised by leptin level < 12 ng/ml with triglycerides ≥ 5.65 mmol/l and/or HbA1c ≥ 6.5 %, in adults and children 2 years of age and above

The indication approved by CHMP was as replacement therapy adjunctive to diet to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

- with confirmed congenital generalised LD (*Berardinelli-Seip syndrome*) or acquired generalised LD (*Lawrence syndrome*) in adults and children 2 years of age and above
- with confirmed familial partial LD or acquired partial LD (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

The recommended daily dose of metreleptin is based on body weight. The starting daily dose for patients weighing under 40 kg is 0.06 mg/kg and a maximum daily dose of 0.13 mg/kg. For male patients weighing more than 40 kg, the starting daily dose is 2.5 mg, whilst for female patients over 40 kg, the starting daily dose is 5 mg. For all patients weighing more than 40 kg, the maximum daily dose is 10 mg.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest for all the patients included in the claimed indications. The CHMP considered that metreleptin could have a high impact in the treatment of patients with generalised lipodystrophy. However, the data submitted in support of partial lipodystrophy had significant limitations in defining the patients which could benefit from metreleptin treatment in this condition especially in terms of threshold values for HbA1c and/or TG. This is further compounded by the fact that conventional therapy with diet, antidiabetics and lipid-lowering drugs could potentially be sufficiently effective in at least some of these patients. The potential for this product to induce production of neutralising antibodies (NAbs) against both metreleptin and endogenous leptin was considered another complicating factor in defining a population with a favourable benefit/risk balance.

- Exceptional circumstances

The Applicant considered that the grounds for marketing authorisation under exceptional circumstances apply to Myalepta according to the Article 14 (8) of Regulation (EC) No 726/2004 and to Part II.6 of Annex I to Directive 2001/83/EC and provided justification based on the inability to provide comprehensive efficacy and safety data due to rarity of indication.

The prevalence for GL (combined congenital and acquired) is estimated to be between 0.01 to <0.15 in 10,000 and the prevalence for PL (combined congenital and acquired) is approximately 0.02 to <0.3 in 10,000. The applicant considered the true prevalence to be at the low end of the range based on available literature and databases.

At present, there are no medicinal products marketed in the EU for the treatment of generalised or partial lipodystrophy.

Given the proposed indication for metreleptin as treatment for patients with GL and for a subset of patients with PL who have more severe metabolic abnormalities, prevalence was also estimated for this PL subgroup. Although the data are limited, the prevalence of this PL subgroup would likely be <0.03 in 10,000. As a result of these estimates, the sample population available for inclusion in clinical trials is extremely limited.

The applicant also noted that, the extreme rarity of the condition resulted in prolonged recruitment for both studies submitted in support of this application.

Study NIH 991265/20010769 took 14 years to enrol these 107 patients, including patients who travelled internationally to participate in the study equating to 0.65 pts/month enrolment rate.

Study FHA101 took 5 years to enrol 41 patients with 6 sites open this equating to an 0.25 pts/month enrolment rate.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as is a powder for solution for injection containing 11.3 mg of metreleptin as active substance (AS).

Other ingredients are glycine, sucrose, polysorbate 20, glutamic acid and sodium hydroxide (for pH adjustment).

The product is available in a type I glass vial (5 ml) with a bromobutyl rubber stopper and an aluminium seal/plastic flip off cap. The finished product comes in a pack size of 1 vial or 30 vials.

2.2.2. Active Substance

General information

Metreleptin is a recombinant human leptin analogue (i.e. recombinant methionyl human leptin) produced in *E. coli* by recombinant DNA technology. It is 147 amino acids long and has a molecular weight of approximately 16 kDa. It is a protein hormone that differs from the human leptin sequence by a single additional amino acid, i.e. methionine, located at the N-terminal end. Metreleptin has one disulfide bond between Cys-97 and Cys-147.

Metreleptin exerts its function by binding to and activating the human leptin receptor, which belongs to the Class I cytokine family of receptors that signals through the JAK/STAT transduction pathway. It acts via multiple mechanisms to decrease triglyceride and other lipid intermediates in lipodystrophy patients, reducing their accumulation in tissues such as liver and muscle, and ameliorating severe insulin resistance, thereby improving hyperglycaemia and hypertriglyceridaemia.

Manufacture, characterisation and process controls

Manufacture and part of the release testing of the metreleptin active substance takes place Sandoz GmbH, Biochemiestrasse 10, Kundl, Austria.

Description of manufacturing process and process controls

The metreleptin AS manufacturing process has the following three sub-processes: inoculum/fermentation, isolation, and purification.

The first sub-process generates cells containing metreleptin that originates from use of a WCB vial expanded in flasks and transferred to the main fermenter. The main fermentation produces the majority of the metreleptin containing cells prior to lysing during the second sub-process. The process has been validated to hold material following the second sub-process prior to starting the third sub-process of purification. The third-sub process of purification includes several steps to form the disulphide bond, purify the Metreleptin, concentrate, formulate with excipients, sterile filter, and fill into a validated container closure system prior to storage.

A description of the container closure system for the metreleptin AS was provided. The container is stated to be in compliance with the Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03) and compatibility of metreleptin with the primary has been demonstrated.

Control of materials

The compendial and non-compendial raw materials used in the manufacturing process are sufficiently described and controlled. Animal-derived materials used in the media and feed solutions of the AS manufacturing process for metreleptin. These animal-derived materials are in compliance with the TSE Note for Guidance. Cells expressing the metreleptin protein were established by transformation and subsequent selection. Generation and testing of the expression were described. A cell banking system was established and adequately tested and qualified in accordance with the requirements of the relevant ICH guidelines. Protocols and acceptance criteria are in place to generate future WCBs. Genetic stability is also addressed in end-of-production cells and extended generation cells and was sufficiently demonstrated.

Manufacturing process development

The manufacturing process was initially developed. A historic overview of the development has been provided and includes details about site transfers, scale changes and overall changes made to the manufacturing processes. Clinical batches were produced including data on physicochemical attributes, impurity profiles, stability study results and batch analysis. The data show that lots can be considered comparable, regardless of the manufacturing site or fermentation scale.

Control of critical steps and intermediates

The production process and process controls are described in detail. Process validation and evaluation have been performed for each sub-process taking into account the results from pre-validation quality risk assessment, which in essence analyses the risk for process failures and defines the classification of the process parameters and the in-process controls, based on platform and process knowledge and on process characterisation studies taking into account their impact on critical quality attributes (CQAs).

The control strategy is considered sufficiently established based on process characterisation studies. The quality of the metreleptin AS is controlled by both in-process controls and release testing.

Process validation

The process validation (PV) batches were manufactured and this represents the main process validation of the entire manufacturing process. This was followed by supplemental validation studies in order to maintain the validated state of the manufacturing process. For the validation assessment and studies were performed in manufacturing campaigns using process parameters, in-process controls, and acceptance criteria in place at the time of manufacture.

The manufacturing process for metreleptin active substance is considered to be adequately validated. Consistency in production has been shown on batches. All acceptance criteria for the critical operational parameters and for the in process controls are fulfilled demonstrating that the process consistently produces metreleptin active substance of reproducible quality that complies with the predetermined specification and in-process acceptance parameters.

Chromatographic Resin reuse was investigated and chromatography resin reuse cycles qualified during process validation.

The transport and shipping of metreleptin AS occurs at and has been fully validated in relation to packaging and shipment procedures.

Characterisation

Metreleptin structure has been confirmed through extensive characterisation testing to verify physicochemical properties, primary, secondary, tertiary and higher order structure, purity and impurities, and biological activity of the metreleptin AS.

The primary structure and composition have been confirmed by a combination of peptide mapping with liquid chromatography/mass spectrometry (LC/MS) detection, amino acid sequence analysis, and MS determination of molecular weight.

The higher order structure was characterised by four different analytical techniques.

The applicant has established a bioassay to determine the biological activity of metreleptin. The metreleptin binds to the target expressed by these cells. The cells proliferate in response to the varying amounts of metreleptin and cell proliferation is quantitated by measuring a signal. The potency is reported relative to the potency of the Reference Standard.

The chemical purity of metreleptin is quantitated. This method also quantitates impurities observed in the FP, including product-related impurities from the AS and metreleptin degradation products. Impurities present are quantitated. Purity and identity are further determined.

Process- and product-related impurities in the AS are also sufficiently addressed.

Metreleptin AS has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure. The analytical results are consistent with the proposed structure and characterisation methods are considered adequate.

Specification

The following list of specifications is proposed for the commercial metreleptin AS.

Descriptions of the analytical procedures used for release and stability testing of the AS have been presented. In addition, standard operating procedures (SOP) have been provided for all analytical procedures appearance by visual inspection, pH, and bacterial endotoxins which are performed according to *Ph.Eur.* requirements**.** Analytical methods have been adequately validated in line with ICH guidelines.

Batch analysis

Batch analysis data of the active substance were provided. In total results for batches have been presented of which the final commercial. The results are within specifications and confirm consistency of the manufacturing process.

Reference material

Qualification of reference standards that were used during product development and reference standards that will be used during commercial production were described in detail.

Stability

A shelf-life is proposed for metreleptin AS, when stored at the recommended condition.

To support the claimed shelf life several stability studies have been performed as follows: Primary stability studies with a number of batches produced at the proposed commercial manufacturing site; supporting stability studies with batches manufactured at a fermentation scale; a number of commercial AS batches and a study to support the storage and shipment of the AS to the FP manufacturing site.

It has been demonstrated that AS batches are comparable regardless of the fermentation scale or manufacturing site, all of the above data has been considered to support the claimed the shelf-life of the AS. In conclusion, stability data for the primary stability batches have been provided. The data

indicate that the AS is stable at the proposed long term storage condition and does not show any sign of degradation or loss of potency.

Comparability exercise for Active Substance

Comparability studies have been conducted between Phase 2, Phase 3 AS batches and AS batches proposed for commercial use. The approach presented by the applicant is considered in line with ICH Q5E guideline. The data demonstrate that pilot scale lots, clinical lots and process validation/commercial lots can be considered comparable, regardless of the manufacturing site or fermentation scale.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Myalepta FP is a sterile, white, solid lyophilised cake containing 11.3 mg metreleptin AS in a 5 mL Type I glass vial. Myalepta contains the following excipients Glycine, Sucrose, Polysorbate 20, L-glutamic acid and Sodium hydroxide (pH adjustment). The quantitative composition of Myalepta finished product has been presented.

Prior to administration via subcutaneous injection, the powder is reconstituted with 2.2 mL of water for injections (WFI) to obtain a final formulation of 5 mg/mL metreleptin. The resulting solution is for single use only. No overage is included in the formulation of Myalepta.

The compendial grade excipients are added during the purification process of AS production and no additional excipients are used in the formulation of the FP. Sufficient information has been provided for the description and composition of the FP.

The FP is stored in Type I glass vial (5 ml) with a bromobutyl rubber stopper and an aluminium seal/plastic flip off cap. The product comes in pack sizes of 1 or 30 vials. The patient will receive a carton containing 1 or 30 vials of Myalepta, depending on the pack size, which should be stored in a refrigerator until the day of use. The patient will also receive separately the solvent for reconstitution (i.e. water for injection), the syringes/needles for reconstitution, the syringes/needles for administration, the cleansing alcohol swabs, and a sharps disposal container.

During the procedure a major objection was raised on the general composition of the product: Myalepta is a powder for solution for injection and proposed to be commercialised without its solvent for reconstitution (i.e. water for injections) and without the syringes to be used for both reconstituting the FP and administering the correct dose. As Myalepta is intended to be administered by the patient himself or by the caregiver the CHMP considered that there could be a risk that the absence of these two components (i.e. solvent for reconstitution and appropriate syringes) can lead to medication errors. The applicant was asked to reconsider its product composition and to include an appropriate presentation of the solvent for reconstitution and appropriate syringes for reconstitution and administration with each presentation of lyophilised FU. It was further requested that the appropriateness of the provided components should be demonstrated in particular regarding the administration of the lowest possible recommended dose (i.e. increment dose of 0.004 mL/kg for children of 2 years of age). The applicant was also encouraged to develop a suitable and user-friendly administration device and, in relation to this, to reconsider the dosage form of the FP if needed.

In the responses the applicant proposed an alternative arrangement to minimise the risk of medication errors and to address the concerns related to the feasibility and accuracy of the lowest

dose to be administered. These measures comprise: 1) provision of separate reconstitution and administration kits; 2) provision of the solvent for reconstitution (i.e. WFI) by the pharmacist; 3) detailed information relating to appropriate syringe size use, use of solvent and instructions on how to reconstitute and administer the correct dose in the SmPC/PIL/instructions for use (IFU); and 4) educational and training materials related to appropriate syringe size use, preparation and dosing as part of the risk management plan (RMP). The educational and training materials also include online video media showing all the steps to preparing and administering Myalepta.

On the basis of the information the CHMP concluded that the measures implemented are adequate to mitigate the risk of medication errors. The pharmaceutical development of the finished product was further considered correctly addressed as it discussed the relevant aspects of the product and process development, and highlighted the critical quality attributes and process parameters. The safety of the container closure system has been appropriately demonstrated by compliance with compendial standards and an appropriate leachable study.

Manufacture of the product and process controls

Manufacture and primary packaging of Myalepta takes place at the manufacturing site. The batch size has been provided.

The FP manufacturing process involves thawing, dilution of bulk and filling.

The successive steps of the manufacturing process are detailed and illustrated by flow charts.

The main steps have been provided along with the associated in-process controls (IPCs) and operating parameters.

After manufacturing, the vials are shipped from for secondary packaging. The vials are stored between 2-8 °C.

The primary packaging of Myalepta consists of a 5 mL glass vial with lyophilisation stopper made of bromobutyl rubber and aluminium seal with plastic flip-off cap. The suppliers for all components are indicated and the glass vial and lyophilisation stopper meet Ph. Eur. requirements. A description of their attributes (i.e. colour, dimensions, material), a representative drawing and a CoA from the supplier have been presented.

The manufacturing process is adequately described and the critical steps and parameters to be controlled in-process are identified. The FP manufacturing process validation was performed on consecutive validation batches of Myalepta. The process validation is deemed appropriate to demonstrate that the commercial process size can perform effectively and reproducibly to obtain a Myalepta finished product that meets its predefined specifications and quality attributes.

Results from in-process control tests which were requested during the reviewing process, were provided by the applicant.

Quality of the FP is controlled by both in-process controls and release testing. Analytical methods were described in detail and were properly validated. QC testing site has been demonstrated.

Product specification

The release specifications of Myalepta finished product have been provided.

Control of the FP covers the main quality attributes and compendial requirements for parenteral preparations. Stated impurities have been studied in nonclinical and clinical studies as relevant.

Justifications have been provided for setting the FP acceptance criteria for the different quality attributes and are based on batches issued from studies, studies and studies. The proposed limits are considered acceptable and in accordance with the ICH Q6B guideline.

Analytical methods

The analytical methods used have been adequately descried and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis results have been provided for batches manufactured to date and used in clinical and non-clinical studies, and for commercial use. The results from all commercial scale batches comply with the proposed commercial acceptance criteria.

Reference materials

A reference standard was developed for Myalepta finished product. It is stored frozen. From this a working reference standard is being introduced. The current working standard is stored under the same conditions as the FP (5 ± 3 °C) in. The qualification of standards is deemed appropriate for their intended use.

Stability of the product

A shelf life of 3 years is proposed by the applicant. The FP should be stored in a refrigerator (2°C–8°C) and the vial kept in the outer carton in order to protect from light. Following reconstitution with water for injections, the medicinal product must be used immediately and cannot be stored for future use.

FP stability studies have been conducted to support the shelf-life of 3 years for the Myalepta FP. Based on the stability data presented, a shelf-life of 3 years is considered acceptable for the FP, when stored at the recommended condition of 2 to 8°C, protected from light.

Adventitious agents

The raw materials from animal origin used in the AS manufacturing process are in compliance with the TSE Note for Guidance. Appropriate measures are taken to prevent microbial contamination in the AS and FP manufacturing processes.

Post Approval Change Management Protocol

As part of the MAA, the applicant submitted a Post Approval Change Management Protocol (PACMP). The subject of this PACMP is the introduction post-MAA approval of 2 new product presentations of the FP (i.e. nominal 5 mg and 2.5 mg) in addition to the currently provided nominal 10 mg presentation. The main difference between the current and proposed presentations is a different per vial, whereas the formulation and general manufacturing process remain the same. Following reconstitution of the 2.5 mg or 5 mg presentation, the solution will have the same as described for the 10 mg presentation. The PACMP is proposed mainly to facilitate use of the product in paediatric patients and to the product following reconstitution, as it is for single use only. A detailed description of the protocol is provided and is generally acceptable and in line with the Q and A on PACMPs (EMA/CHMP/CVMP/QWP/586330/2010).

Since concerns were raised during the procedure relating to the general composition of the FP in the 10 mg presentation, these would also be applicable to the additional 2.5 mg and 5 mg presentations. Therefore, as a minimum, measures that were implemented for the 10 mg

presentation should also be applied to the new proposed presentations. This is even more critical when considering the very small injection volumes to be administered to paediatric patients, since these new presentations are developed to facilitate dosing of paediatric patients. The applicant states that the 2 additional presentations will also be supplied with administration sets and instructions. The introduction of vials containing 2.5 mg and 5 mg of metreleptin - via a variation procedure following granting of the MA - addresses one of Myalepta's Paediatric Investigation Plan (PIP) commitments to facilitate dosing to paediatric patients.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The AS and FP manufacturing process and process controls are described in detail. Raw materials are sufficiently described and controlled. A system was established and properly tested and qualified. Critical process parameters were identified, including the applicant's rationale for selection of the parameters as critical or non-critical and their associated characterisation or acceptable ranges. The control strategy is considered sufficiently established based on process characterisation studies and quality risk assessments, and taking into account the impact on CQAs such as protein concentration, purity, host cell proteins (HCP), and content. Upon request, the applicant has satisfactorily addressed some important issues as regards the manufacturing process validation, and classification of process parameters. Other validation studies regarding hold time of process intermediates, impurity clearance, column lifetimes, membrane reuse and sanitisation, additional microbiological controls, and shipping qualification are also performed. For some of these studies, additional information originally requested has been further presented.

The AS and FP specifications proposed by the applicant are deemed suitable to control the quality of AS and FP. The proposed acceptance criteria for some AS quality attributes needed further explanation and/or justification, i.e. the proposed acceptance criteria related to total oligomer content, purity and specified impurities and host cell proteins. However, these concerns have been sufficiently addressed and for some quality attributes, tightened acceptance criteria were proposed.

Stability for AS and FP have been investigated with a number of batches. Since comparability between these batches has been demonstrated, the overall long term stability data obtained support the proposed shelf-life of 3 years for the FP.

Besides the other concerns, a major objection was originally identified concerning the general composition of the product. Myalepta is a powder for solution for injection that is proposed to be commercialised without its solvent for reconstitution (i.e. WFI) and without the syringes to be used for both reconstituting the finished product and administering the correct dose. Myalepta is intended to be administered by the patient himself or by the care giver. A substantial risk that the absence of these two components (i.e. solvent for reconstitution and appropriate syringes) can lead to medication errors was identified. In line with the principles outlined in the Good practice guide on risk minimisation and prevention of medication errors (EMA/606103/2014), the applicant was thus asked to revise its product composition and to include an appropriate presentation of the solvent for reconstitution and appropriate syringes for reconstitution and administration with each presentation of lyophilised finished product. The appropriateness of the provided components should be demonstrated in the relevant sections of the dossier, e.g. the fact that the administration of the lowest possible recommended dose (i.e. increment dose of 0.004 mL/kg for children of 2 years of age) is feasible and accurate using the provided syringes. In particular, syringes allowing dosing of

volumes smaller than 0.1 mL are not commonly available. Thus, it was requested that the solvent for reconstitution and syringes should either be supplied with the product.

In his response to the major objection raised, the applicant did not include an appropriate presentation of the solvent for reconstitution and appropriate syringes for reconstitution and administration with each presentation of lyophilised Myalepta finished product. Instead the applicant proposed an alternative arrangement to minimise the risk of medication errors and to address the concerns related to the feasibility and accuracy of the lowest dose to be administered. In summary, these measures comprise: 1) provision of separate reconstitution and administration kits; 2) provision of the solvent for reconstitution (i.e. WFI) by the pharmacist; 3) detailed information relating to appropriate syringe size use, use of solvent and instructions on how to reconstitute and administer the correct dose in the SmPC/PIL/IFU; and 4) educational and training materials related to appropriate syringe size use, preparation and dosing as part of the RMP. The measures currently proposed by the applicant are deemed suitable for mitigating the risk of medical errors.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Metreleptin is a recombinant human leptin analogue produced in *Escherichia coli* cells to express recombinant methionyl-human leptin (r-metHuLeptin). It differs from native human leptin by the addition of a methionine residue at its amino terminus. Native human leptin is produced in, and secreted primarily from, the adipocytes of white adipose tissue.

Nonclinical safety studies on metreleptin were designed to be consistent with relevant EU guidelines, in particular ICH Guideline S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, Addendum, 12Jun2011. All pivotal nonclinical safety studies were compliant with the then-current Good Laboratory Practice (GLP) requirements.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary PD studies with human metreleptin and/or murine metreleptin were conducted *in vitro* and *in vivo* using leptin-deficient, euleptinemic and hyperleptinemic animals, and in dyslipidemic/atherosclerotic models.

In vitro

The potency of metreleptin and recombinant human leptin was investigated in study REC-00111, using the 32D OBECA cell line which was engineered to contain the human leptin receptor. Metreleptin and human leptin had comparable dose-dependent responses in activating the human leptin receptor and subsequent STAT5 phosphorylation. Additionally, metreleptin and recombinant human leptin demonstrated effectively identical stimulation of ATP production by the two molecules in 32D OBECA and equivalent sensitivity to an interfering antibody (data not shown). Results from this study indicated that metreleptin is biologically equivalent to recombinant human leptin.

In vivo

A summary of the primary PD studies conducted in various disease models are summarised in **Table 1.**

The models used included ob/ob which are leptin deficient mice, mice deficient for apolipoprotein E (APOE) and apolipoprotein B48 (APOB48) [Apoe–/– Apob100/100ob–/–]. In addition, the combination of leptin deficiency, altered lipoprotein secretion and absence of the low density lipoprotein receptor (LDLR) was studied in mice having a simultaneous knockout of the genes for leptin, ApoB48, and LDLR [Ldlr–/–Apob100/100 ob–/–].

Table 1. Summary of Primary Pharmacodynamic Studies with Metreleptin-*In vivo* studies in disease models

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
Time of Onset for r-metMuLeptin Effects on Body Mass, Appetite and Metabolic Indices in *ob/ob* and Lean C57BL/6J Mice (REST070335-R2005083)	*ob/ob* mice	Time of efficacy onset	Mice were administered PBS or murine metreleptin at 10 mg/kg/day, q.d., s.c.; mice were sacrificed at 1 h, 3 h, 24 h, 1 week, or 3 weeks after the onset of treatment (n = 5/group).	3 h post-treatment metreleptin reduced food intake and serum triglycerides. 24 h post-treatment metreleptin reduced food intake, serum glucose and insulin. 1- and 3-weeks post-treatment metreleptin reduced food intake, body fat, serum glucose, insulin, cholesterol, triglycerides, glycerol, NEFA, and BHBA, as well as, liver cholesterol, glycerol, and NEFA.
Dose Response Effects of r-metMuLeptin on Metabolic Parameters of Obese *ob/ob* Mice (REST070332-R2005080)	*ob/ob* mice	Dose response effects on metabolism	Female mice were administered PBS or murine metreleptin at (0.0008, 0.003, 0.012, 0.05, 0.2, 0.8, and 3.2 mg/kg/day) via s.c. continuous infusion for 7 days (n = 6/group).	Metreleptin infusion dose-dependently reduced body weight, body fat, serum glucose, insulin, cholesterol, triglycerides, BUN, and platelet count.
Effects of r-metMuLeptin, the Obese Gene Product, on Body Weight Regulation in *ob/ob* Mice (REST070339-R2005087)	*ob/ob* mice	Effects on metabolism	Mice were administered PBS or murine metreleptin by daily i.p. injections (0.1, 1.0, or 10 mg/kg/day) for 28 days (n = 8-10/group).	Metreleptin injections dose-dependently reduced body weight, body fat, food intake, serum insulin and glucose.
Effect of r-metMuLeptin on Atherosclerosis in Leptin Deficient *Apoe*$^{-/-}$ *Apob*$^{100/100}$ *ob*$^{-/-}$ and *Ldlr*$^{-/-}$ *Apob*$^{100/100}$*ob*$^{-/-}$ Mice (REST070349-R2005654)	*Apoe*$^{-/-}$ *Apob*$^{100/100}$ *ob*$^{-/-}$ (male)	Effect on atherosclerosis	Mice were administered murine metreleptin at doses titrated to prevent weight gain (0.02 to 0.08 mg/kg/day, i.p.) or saline for 86 days (n = 7-8/group).	Murine metreleptin lowered plasma cholesterol and reduced atherosclerotic plaques.
Effect of r-metMuLeptin on Atherosclerosis in Leptin Deficient *Apoe*$^{-/-}$ *Apob*$^{100/100}$ *ob*$^{-/-}$ and *Ldlr*$^{-/-}$ *Apob*$^{100/100}$*ob*$^{-/-}$ Mice (REST070349-R2005654)	*Ldlr*$^{-/-}$ *Apob*$^{100/100}$ *ob*$^{-/-}$ (male)	Effect on atherosclerosis	Mice were administered murine metreleptin at doses titrated to prevent weight gain (0.01 to 0.12 mg/kg/day, i.p.) or saline for 86 days (n = 9-13/group).	Murine metreleptin lowered plasma insulin, triglyceride, and cholesterol; improved glucose tolerance; and reduced atherosclerotic plaques.

BHBA = beta-hydroxybutyric acid; BUN = blood urea nitrogen; GLP = Good Laboratory Practice; NEFA = non-esterified fatty acid; i.p. = intraperitoneal; q.d. = once daily; PBS = phosphate buffered saline; s.c. = subcutaneous

A number of primary PD studies were conducted in wild type mice **Table 2**, rats **Table 3** and dogs **Table 4**.

Table 2. Summary of Primary Pharmacodynamic Studies with Metreleptin-*In vivo* studies in mice

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
A Comparison of Various Dosing Regimens of r-metHuLeptin and Efficacy of r-metHuLeptin Versus r-metMuLeptin Via Continuous Infusion in Lean CD1 Mice (REST070331-R2005079)	CD-1 mice (female)	Efficacy of various dosing regiments of human metreleptin in CD-1 lean mice and comparative efficacy of human and murine metreleptin.	Administration of human metreleptin at 0, 0.03, 0.3, 1, or 3 mg/kg/day s.c. b.i.d. or via continuous infusion, or 20 mg/kg/day q.d. bolus injection for 13 days (n = 5-8/group); administration murine metreleptin at 0, 0.03, 0.1, 0.3, or 1 mg/kg/day via continuous s.c. infusion for 31 days (n = 7-9/group)	A regimen of 0.3 to 3 mg/kg/day b.i.d. human metreleptin elicited similar weight loss (~12%) as infusion of murine metreleptin. Final weight loss was greater after continuous infusion of murine metreleptin (13% at 1 mg/kg/day) than after human metreleptin (7% at 1 mg/kg/day).
The Effects Of r-metMuLeptin on Body Weight, Carcass Composition and Serum Chemistry in a Population of 10-Month-old CD1 Female Mice With Various Body Weights and Leptin Levels (REST070334-R2005082)	CD-1 mice (female)	Metabolism of mice of various obesity and leptin levels	Administration of murine metreleptin at 0 or 3 mg/kg/day s.c. b.i.d. for 16 days to mice stratified into different "bins" based on their body weight (n = 6-12/bin).	Murine metreleptin administration reduced body weights in some groups and reduced serum triglycerides in groups with lowest serum leptin levels and lowest baseline body weights.

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
Efficacy of Exogenous Recombinant Murine Leptin in Lean and Obese 10- to 12-month-old Female CD1 Mice (REST070337-R2005085)	CD-1 mice (female)	Effect on metabolism of lean and obese mice	Obese and lean mice received either PBS or murine metreleptin (2.4 mg/kg/day) via continuous s.c. infusion for 7 days. A third group of mice were pair-fed to the respective leptin-treated group (n = 6-8/group).	Murine metreleptin reduced food intake and decreased body weight (mean 3.82 g decrease in obese mice compared to 1.70 in vehicle and 3.3 for control group, and 4.3g, 0.25 and 4.75, respectively in lean mice after 7 days). Serum triglycerides levels in the metreleptin-treated group were reduced, as were those of the pair-fed non-treated mice groups. The half-maximal effective doses for weight loss and fat reduction were shifted 0.5-0.7 log to the right for obese mice. Recombinant murine leptin was less efficacious at low doses (1-3 mg/kg) in obese mice but equal to or more efficacious in obese than lean mice at high doses (30 mg/kg to 100 mg/kg).
Time of Onset for r-metMuLeptin Effects on Body Mass, Appetite and Metabolic Indices in ob/ob and Lean C57BL/6J Mice (REST070335-R2005083)	C57BL/6J mice	Time of efficacy onset	Mice were administered with PBS or murine metreleptin at 10 mg/kg/day, q.d., s.c., or as 6.3 mg/kg/day continuous infusion. Mice receiving metreleptin were sacrificed at 1 h, 3 h, 24 h, 1 week, or 3 weeks after the onset of treatment (n = 5/group).	At 24-h timepoint body weight was reduced by metreleptin. At 1- or 3-week timepoints body weight, liver cholesterol, and triglycerides were reduced.

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
The Role of Estradiol in Mediating Effects of r-metMuLeptin on Adiposity and Body Weight in C57BL/6J Mice (REST070338-R2005086)	C57BL/6J mice (female)	Metabolism of OVX mice	OVX and intact mice were subdivided into 6 dose groups receiving murine metreleptin via continuous s.c. infusion at 0, 0.02, 0.07, 0.28, 1, and 7 mg/kg/day for 14 days (n = 5-6 mice/group).	Normal and OVX mice exhibited reduced body fat, cholesterol, and serum triglycerides at murine metreleptin doses of 1 and 7 mg/kg/day.
	C57BL/6J mice (female)	Metabolism of OVX mice treated with estradiol	OVX and intact mice were treated with a combination of 17-estradiol (17 µg/day s.c. pellets) and murine metreleptin (7mg/kg/day, continuous s.c. infusion) for 14 days (n = 5-6 mice/group).	Murine metreleptin reduced body fat, serum triglycerides, and cholesterol with or without estradiol cotreatment.
Physiological Response to Long-term Peripheral and Central Recombinant Murine Leptin (r-metMuLeptin) Infusion in Lean and Obese Mice (REST070329-R2005073)	Lean C57BL/6J, AKR/J, NZO, C57BL/6J A^y mice	Energy Balance in various murine obesity models	Lean C57BL/6J mice were administered murine metreleptin via continuous s.c. infusion (0, 200, 300, 400, or 500 ng/h equivalent to 0, 5, 7, 10, or 12 µg/day) for 14 days (n = 8/group). NZO, A^y, and AKR/J mice received high-dose i.p. injections (12.5 mg/kg b.i.d.) or continuous s.c. infusion (0.5 to 5 µg/h) of murine metreleptin (n = 5-8/group).	Murine metreleptin reduced body weight in lean and AKR/J mice, but had no effect on NZO and A^y mice.
Effects of r-metMuLeptin, the Obese Gene Product, on Body Weight Regulation in *ob/ob* Mice (REST070339-R2005087)	C57BL/6J mice	Effects on metabolism	Mice were administered murine metreleptin by daily i.p. injections (0, 0.1, 1.0, or 10 mg/kg/day) for 28 days (n = 8-10/group).	Murine metreleptin dose-dependently reduced body weight, body fat, and food intake.

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
The Effects of r-metMuLeptin on Body Weight, Carcass Composition and Serum Chemistry in Obese (old) and Lean (young) CD1 Mice (REST070333-R2005081)	CD 1 mice (female)	Metabolism of lean and obese mice	Obese and lean CD-1 mice received PBS or murine metreleptin (1, 3, 10, 30, or 100 mg/kg/day) as twice daily bolus i.p. injections for 14 days (n = 4-6/group).	At metreleptin doses as low as 3 mg/kg/day, both lean and obese mice had triglyceride levels that were 30% to 50% lower than their respective control group. Doses of 10 to 100 mg/kg/day also lowered triglycerides and body weight.
Efficacy of Exogenous Recombinant Murine Leptin in Lean and Obese 10- to 12-month-old Female CD1 Mice (REST070337-R2005085)	CD 1 mice (female)	Effects of 1-month treatment on metabolism of lean and obese mice	Obese and lean CD-1 mice received PBS or murine metreleptin (1, 3, 10, 30, or 100 mg/kg/day, q.d.) as daily bolus i.p. injections for 33 days (n = 5-6/group).	Metreleptin sensitivity was moderately reduced in obese vs. lean CD-1 mice (e.g., half-maximal dose for weight and fat is 0.5-0.7 log shifted to the right in obese mice).
Metabolic and Behavioral Effects of Centrally Administered r-metMuLeptin on CD1 Mice and Sprague-Dawley Rats (REST070336-R2005084)	CD 1 mice (male), SD rats	CNS administration-effects on metabolism	Mice received PBS or murine metreleptin (0.03, 0.1, 0.3, 1.0, or 3.0 µg/day) as daily (q.d.) free-hand bolus i.c.v. injections for 10 days (n = 4-5/group).	Murine metreleptin doses of 0.03 to 3.0 µg/day reduced body weight.
	CD 1 mice (male), SD rats	CNS administration-effects on metabolism	Mice received PBS or murine metreleptin (0.3 µg/day) as bolus i.c.v. injections daily (q.d.), every other day (q2d), or every third day (q3d) for 13 days (n = 4--5/group for PBS-treated and 9-10/group for murine metreleptin - treated groups).	Murine metreleptin i.c.v. q.d., q2d, or q3d reduced body weight, serum triglycerides, and NEFA.

REST070336-R2005084 (continued)	CD 1 mice (female), SD rats	CNS administration-effects on metabolism	Obese and lean CD-1 mice received PBS or murine metreleptin (0.1, 1, or 3 µg/day) as bolus i.c.v. injections daily (q.d.) for 11 days (n = 5/group).	Murine metreleptin i.c.v. reduced body weight in lean and obese mice at all doses. Serum leptin was reduced in obese mice at all administered doses. Serum glucose was reduced in lean mice only.
Physiological Response to Long-term Peripheral and Central Recombinant Murine Leptin (r-metMuLeptin) Infusion in Lean and Obese Mice (REST070329-R2005073)	Lean C57BL/6J, NZO, C57BL/6J A^y mice	Energy balance in various murine obesity models	Lean C57BL/6J mice received PBS or murine metreleptin (8 ng/h equivalent to 0.2 µg/day) as i.c.v. infusion for 30 days (n = 6/group). NZO and A^y mice received murine metreleptin i.c.v infusion at 5, 50, or 500 ng/h (n = 5/group).	Murine metreleptin i.c.v. administration resulted in substantial weight loss in lean and NZO mice, but had minimal effect in A^y mice.

Table 3. Summary of Primary Pharmacodynamic Studies with Metreleptin-*In vivo* studies in rats

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
Effect of r-metMuLeptin on Visceral Adiposity and In Vivo Insulin Action in Sprague-Dawley Rats (REST070343-R2005091)	SD rats	Visceral adiposity and insulin action	Male SD rats received PBS or murine metreleptin (0.5 mg/kg/day) via continuous s.c. infusion for 8 days (n = 6-7/group).	Murine metreleptin markedly reduced visceral adiposity and enhanced whole body insulin action (inhibition of glucose production, stimulation of glucose uptake).
Characterization of the Interaction Between r-metMuLeptin and Thyroid Hormones in the Regulation of Energy Metabolism in Sprague-Dawley Rats (REST070347-R2005101)	SD rats	Metabolism of thyroidectomized rats	Male SD rats received PBS or murine metreleptin (0.3 mg/kg/day) via continuous s.c. infusion for 3 weeks in the presence or absence of thyroid hormone replacement (n = 8-10/group).	Murine metreleptin reduced body weight, serum triglycerides, and cholesterol with or without thyroid hormone replacement.
Differential Effects of r-metMuLeptin in Regulation of Tissue Glucose Utilization In Vivo in Normal Sprague-Dawley Rats (REST070345-R2005099)	SD rats	Glucose utilization	Normal male SD rats received PBS or murine metreleptin (4 mg/kg/day) via continuous s.c. infusion for 5 days (n = 8-12/group).	Glucose uptake was enhanced into muscle and reduced into white adipose tissue.
Effect of r-metMuLeptin on Glucose Metabolism in Streptozotocin-induced Insulin-deficient Diabetic Rats (REST070346-R2005100)	SD rats	Metabolism of streptozotocin-induced diabetic rats	Insulin-deficient male SD rats received PBS or murine metreleptin (4 mg/kg/day) via continuous s.c. infusion for 12 to 14 days (n = 10/group).	Murine metreleptin reduced hyperglycemia and hypertriglyceridemia; improved whole-body glucose turnover and reduced glucose production. Results suggested a potent anti-diabetic effect of metreleptin.
Effect of r-metMuLeptin Administration on Skeletal Muscle Insulin Responsiveness in Diet-induced Insulin-resistant Rats (REST070330-R2005074)	Wistar rats	Insulin secretion in high fat-fed rats	Male Wistar rats received PBS or murine metreleptin (10 mg/kg/day) as s.c. b.i.d. injections for 15 days (n = 10-12/group).	As murine metreleptin had no effect on glucose- or tolbutamide-induced insulin secretion, changes in whole body glucose tolerance may arise due to changes in insulin sensitivity as opposed to secretion.
	Wistar rats	Muscle insulin response of high fat-fed rats	Male Wistar rats received PBS or murine metreleptin (10 mg/kg/day) as s.c. b.i.d. injections for 12 days (n = 7-8/group).	Murine metreleptin normalized intramuscular triglyceride levels and hindlimb glucose uptake in insulin resistant muscles.
	Wistar rats	Glucose utilization of high fat-fed rats	Male Wistar rats received PBS or murine metreleptin (10 mg/kg/day) as s.c. b.i.d. injections for 12 days (n = 5-6/group).	Murine metreleptin improved insulin-induced whole body glucose clearance in glucose-intolerant rats.

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
Effect of Chronic r-metMuLeptin Treatment on Triglyceride Production in Normal Sprague-Dawley Rat (REST070348-R2005102)	SD rats	Triglyceride synthesis	Female SD rats received PBS or murine metreleptin (10 mg/kg/day) as i.p. b.i.d. injections for 4 to 5 days (n = 8-11/group).	Murine metreleptin administration decreased basal plasma triglyceride levels and in -vivo triglyceride production.
Short-term Effects of r-metMuLeptin on Hepatic Gluconeogenesis and in Vivo Insulin Action in Sprague-Dawley Rats (REST070341-R2005089)	SD rats	Hepatic glucose production	Male SD rats were administered PBS or murine metreleptin (0.3 mg/kg/h) via continuous i.v. infusion for 6 hours (n = 8-12/group).	Murine metreleptin i.v. enhanced insulin-induced suppression of glucose production by inhibiting glycogenolysis. Metreleptin had no effect on whole body glucose uptake and utilization.
Effect of Intracerebroventricular Administration of r-metMuLeptin on Hepatic and Peripheral Glucose Fluxes in Sprague-Dawley Rats (REST070342-R2005090)	SD rats	Hepatic glucose production	Male SD rats received PBS or murine metreleptin (0.02 or 1 µg/kg/h) via continuous i.c.v. infusion for 6 hours (n = 7-9/group).	Murine metreleptin i.c.v. suppressed hepatic glycogenolysis, but had no effect on whole body glucose uptake and utilization. Regulation of hepatic glucose fluxes was largely mediated by central receptors.
Metabolic and Behavioral Effects of Centrally Administered r-metMuLeptin on CD1 Mice and Sprague-Dawley Rats (REST070336-R2005084)	SD rats	CNS administration-effects on metabolism	Female SD rats received PBS or murine metreleptin (0.03, 0.1, 0.3, 1, 3, or 10 µg/day) via continuous i.c.v. infusion for 14 to 16 days (n = 5-6/group).	Murine metreleptin (0.03-10 µg/day, i.c.v.) reduced food intake for 3 to 7 days. Fat weight and serum triglycerides were reduced by the end of the dosing period. Doses of 0.1 to 10 µg/day reduced body weight and serum cholesterol.
Effect of Intracerebroventricular Administration of r-metMuLeptin on Insulin Sensitivity and Systemic Glucose Uptake in Normal Sprague-Dawley Rats (REST070344-R2005098)	SD rats	CNS administration-effects on metabolism	Female SD rats were administered Dulbecco's PBS or murine metreleptin (10 µg/day) via bolus i.c.v. injection (acute and subacute [overnight] studies) or continuous i.c.v. infusion (chronic study) for 7 days (n = 5-7/group).	Murine metreleptin i.c.v. increased insulin sensitivity and systemic glucose utilization with effects evident as early as 16 h post-treatment. Effects wewere even more pronounced after 7 days of treatment.

Table 4. Summary of Primary Pharmacodynamic Studies with Metreleptin-*In vivo* studies in dogs

Study Title (Report No.)	Species / Strain	Objective	Methods	Noteworthy Findings
A Combined Dietary Restriction and Subcutaneous Injection Study of Recombinant-Methionyl Human Leptin (r-metHuLeptin) in Obese Female Beagle Dogs (REST070195-55014)	Beagle dogs	Metabolism of obese dogs	Human metreleptin was injected s.c. at a total daily dose of 0 (n=3), 0.15 mg/kg (n=3), or 5.0 mg/kg (n=4) to obese female Beagle dogs. Prior to metreleptin treatment, the dogs were 47-day diet restricted (to lose 25% absolute body fat content). They were then treated for 28 consecutive days followed by a 30-day diet restriction period during which they were not dosed, followed by a second 28-day treatment period followed by a 28-day recovery period.	Doses of human metreleptin up to 5.0 mg/kg/day for 28 days was not sufficient to maintain the weight and fat content obtained following severe diet restriction in obese female Beagle dogs.
A 3-week Subcutaneous Injection Pharmacology Study of Recombinant-Methionyl Human Leptin (r-metHuLeptin) in Obese and Lean Beagle Dogs (REST070350-55631)	Beagle dogs	Metabolism of lean and obese dogs; pilot study	Female lean and obese Beagle dogs received s.c. injections of human metreleptin (15 mg/kg/day) for 3 weeks (n = 6/group).	Marked loss of food intake and body weight in lean and obese dogs at the high dose of human metreleptin.
A 28-Day Subcutaneous Injection Dose-Scheduling Study of Recombinant-Methionyl Human Leptin (r-metHuLeptin) in the Beagle dog Followed by a 28 Day Recovery Period (REST070190-54841)	Beagle dogs	Metabolism of lean dogs	Human metreleptin was injected s.c. at a total daily dose of 0 (1 male, 2 females), 0.3 mg/kg either as 0.1 t.i.d. (2 males, 2 females), 0.15 b.i.d. (1 male, 3 females), 0.3 q.d. (1 male, 3 females) for 28 days, followed by a recovery period of 28 days.	Dogs treated with metreleptin showed a loss in body weight which ranged from 21 to 30%. No conclusive evidence of a difference between q.d.., b.i.d. or t.i.d. regimens. During recovery, effects on body weight and composition were reversible.

b.i.d. = twice daily; CNS = central nervous system; i.c.v. = intracerebroventricular; i.p. = intraperitoneal; i.t. = intrathecal; i.v. = intravenous; NEFA = non-esterified fatty acids; OVX = ovariectomized; PBS = phosphate buffered saline; q.d. = once daily; q2d = every other day; q3d = every third day; s.c. = subcutaneous; SD = Sprague-Dawley

Secondary pharmacodynamic studies

In study REST070340-R2005088, the effect of metreleptin on wound healing was investigated. Wounds were made on the dorsal surface of female *ob/ob* and *db/db* mice. *db/db* mice have the same phenotype as *ob/ob* mice but lack a functional leptin receptor. A significant decrease in wound size was observed in metreleptin-treated *ob/ob* mice compared to controls. No decrease was observed in *db/db*.

Metabolic and behavioural effects of metreleptin on Sprague-Dawley rats were investigated in study REST070336-R2005084. At doses that induce significant suppression of appetite, mazindol, fenfluramine, and amphetamine, all elicited substantial increases in locomotor activity as expected. In contrast, murine metreleptin, when administered at high doses by either the i.p. (1 to 30 mg/kg) or i.c.v. routes (1 to 10 µg/day continuous infusion for 3 days) did not elicit any change in the ambulatory activity of the rats.

Safety pharmacology programme

The potential adverse effects of metreleptin on different physiological systems were evaluated in a GLP-compliant battery of safety pharmacology studies, and are summarised in **Table 5.**

Table 5. Summary of Safety Pharmacology studies conducted with metreleptin

Organ Systems Evaluated	Species	Method of Admin	Doses (mg/kg)	Gender/ number per group	Major Findings	Study Reference
CNS: Irwin test	CD-1 mice	s.c.	0, 3, 10, 30 and clonidine HCl	Males / 6 5 groups	Metreleptin administered generally had no effects in the Irwin Test and no effects on respiration rate and body temperature when assessed over a 24 h post-dosing period.	REST070279-GAN00101
CNS: rotarod performance	SD rats	s.c.	0, 3, 10, 30 and chlorpromazine HCl	Males / 8 5 groups	At 30 minutes after dosing, metreleptin had no effect on rotarod performance (relative to vehicle)	REST070271-GAN00111
CNS: grip strength	SD rats	s.c.	0, 3, 10, 30 and chlorpromazine HCl	Males / 8 5 groups	Metreleptin had no effect on grip strength. suggesting it had no effect on muscle tone.	REST070276-GAN00110
CNS: locomotor activity	SD rats	s.c.	0, 3, 10, 30 and chlorpromazine HCl	Males / 8 5 groups	At 30 minutes after dosing, metreleptin had no effect on locomotor activity (relative to vehicle)	REST070277-GAN00104
CNS: tail flick latency	SD rats	s.c.	0, 3, 10, 30 and morphine sulphate	Males / 10 5 groups	At 30 minutes after dosing, metreleptin had no effect on tail flick latency (relative to vehicle), suggesting that metreleptin had neither anti- nor pronociceptive effects at the doses tested.	REST070273-GAN00103

Organ Systems Evaluated	Species	Method of Admin	Doses (mg/kg)	Gender/ number per group	Major Findings	Study Reference
CNS: anticonvulsant and proconvulsant effects	CD-1 mice	s.c.	0, 3, 10, 30 and chlordiazepoxide HCl 0, 3, 10, 30 and picrotoxin	M / 10 10 groups	No anti- and proconvulsant effects were observed. Metreleptin had anticonvulsant activity, but no effect on the proconvulsant test. Metreleptin 10 mg/kg s.c. induced a statistically significant increase in the latency to onset of clonic seizure activity in the anticonvulsant test. The effects of metreleptin at 30 mg/kg were similar to those at 10 mg/kg in magnitude; they were not statistically significant. Mice did not experience clonic convulsions after treatment with 10 and 30 mg/kg metreleptin.	REST070262-GAN00102
CNS: influence on hexobarbital effects	CD-1 mice	s.c.	0, 10, 30 and chlorpromazine HCl	M / 6 4 groups	Metreleptin had no effect on the duration of sleep induced by hexobarbital or on the time taken for the loss of the righting reflex to occur indicating that metreleptin does not modify the anesthetic actions of hexobarbital in mice.	REST070299-GAN00105
Cardiovascular	Beagle dogs	s.c.	0, 5, 25	M / 9 3 groups	No effects on the hemodynamic parameters were observed following a single administration of metreleptin.	REST070255-93063
Cardiovascular	SD rats	s.c.	0, 3, 10, 30	M / 7 1 group (dose-escalation from 0 to 30 mg/kg on days 1-4)	In unanesthetized, telemetered male rats, metreleptin had no obvious effect on resting blood pressure and heart rate over 24 h. The only statistically significant differences from the vehicle time-matched control data occurred during the cardiovascular response to the dosing procedure, with a diminution of the pressor response and tachycardia following a dose of 3 mg/kg. As this did not occur following higher doses, it is not considered to be a pharmacological effect of metreleptin treatment.	REST070275-GAN00109

Organ Systems Evaluated	Species	Method of Admin	Doses (mg/kg)	Gender/ number per group	Major Findings	Study Reference
Renal	SD rats	s.c.	0, 3, 10, 30 and furosemide	M / 8 x 5 groups	Metreleptin had no effect on the volume or pH of urine in saline-loaded male rats. Treatment with 10 mg/kg metreleptin was associated with a minimal increase in urine potassium and chloride concentrations 3 h post-dose. At 6 h post-treatment 30 mg/kg metreleptin resulted in a decrease in urine sodium and chloride levels.	REST070278-GAN00108
Gastrointestinal tract	SD rats	s.c.	0, 3, 10, 30 and morphine sulpharte	M / 10 5 groups	Metreleptin had no effect on either gastrointestinal transit or gastric emptying relative to the reference substance, morphine sulfate.	REST070272-GAN00106
Gastrointestinal tract	Dunkin-Hartley guinea-pigs, isolated ileum	NA	0, 0.5, 5, 50 µg/mL	NA	Metreleptin exhibited no direct contractile effect.Over this same concentration range, metreleptin had no effect on responses to acetylcholine, histamine, 5-hydroxytryptamine, or barium chloride.	REST070274-GAN00107

Pharmacodynamic drug interactions

No pharmacodynamic interaction studies were submitted, but the applicant acknowledged the established risk of hypoglycemia in patients treated with metreleptin who are on high doses of insulin or insulin secretagogues.

2.3.3. Pharmacokinetics

The pharmacokinetic (PK) profile of metreleptin has been assessed in mice, dogs, and sheep. The studies in mice included normal, bilaterally nephrectomised, and pregnant animals, and examined the PK profiles of metreleptin following s.c. or intravenous (i.v.) administration. The PK profile of metreleptin was evaluated in dogs following s.c. and i.v. administration and in sheep following s.c. or i.v. injection. Toxicokinetic (TK) analyses were also conducted in GLP toxicity studies in mice and dogs.

Absorption

Mice

PK data were collected after single s.c. and i.v. dosing **Table 6** and repeat dosing up to 14 days **Table 7** in CD-1 mice.

Table 6. Single-Dose TK Study in CD-1 Mice, Study REST070295-OBH.036

Route	Dose	T_{max} (h)	C_{max} (ng/mL)	AUC (ng•h/mL)	$T_{1/2}$ (h)	F	V_{ss} (mL/kg)	CL (mL/h/kg)
s.c.	0.3	0.28	377	348	0.408	0.71	-	-
	1	0.14	1520	1230	0.388	0.84	-	-
	3	0.50	3810	3780	0.379	0.83	-	-
	10	0.39	12600	14000	0.436	0.89	-	-
i.v.	0.3	-	-	491	0.446	-	142	611
	1	-	-	1470	0.491	-	146	681
	3	-	-	4530	0.484	-	171	663
	10	-	-	15800	0.476	-	158	633

s.c.: subcutaneous, i.v.: intravenous, AUC: area under the curve,F: bioavailability, Vss: Volume of distribution at steady-state, CL: clearance

Table 7. Repeat-Dose TK Study inCD-1 Mice, Study REST070295-OBH.036

Dose (mg/kg)	T_{max} (h)			C_{max} (ng/mL)			AUC (ng•h/mL)		
	D1	D7	D10	D1	D7	D10	D1	D7	D10
1	0.167	0.28	0.39	1440	1393	1534	1263	1453	1891
10	0.39	0.5	0.28	10700	12480	14700	10256	12644	17937

Dogs

Following single-dose s.c. administration at 0.3 or 3 mg/kg in Beagle dogs, serum recombinant human metreleptin concentrations increased moderately rapidly **Table 8**.

Table 8. Single-Dose TK Study in male Beagle dogs, Study REST070292-P792

ROUTE	DOSE (mg/kg)	T_{max} (h)	C_{max} (ng/mL)	AUC (ng•h/mL)	$T_{1/2}$ (h)	F	V_{ss} (mL/kg)	CL (mL/h/kg)
s.c.	0.3	2.8	180	1320	2.1	0.9	-	-
	3	4	1080	11700	2.7	0.7	-	-
i.v.	0.3	-	-	1450	1.16	-	193	215
	3	-	-	16400	1.46	-	165	194

Following multiple s.c. administration of recombinant human metreleptin at 0.3 or 3 mg/kg in dogs, there was a 2-fold increase in AUC from Day 1 to Day 13 **Table 9**. There was no gender-related difference in the PK of metreleptin.

Table 9. Repeat-Dose TK Study in Beagle dogs (Males and Females), Study REST070291-P793

DOSE	T_{max} (h)			C_{max} (ng/mL)			AUC (ng•h/mL)		
	D0	D6	D13	D0	D6	D13	D0	D6	D13
0.3	4	2.5	2	155	194	361	1220	1240	2520
3	4	2.5	2.3	1440	2180	2750	11500	13500	21600

Sheep

The PK profile of recombinant human metreleptin was also characterised in Merino wethers sheep following a single i.v. (0.10 mg/kg) or s.c. (0.15 mg/kg) dose (Study REST070284-101535). Following i.v. administration, serum concentrations of metreleptin declined in a biphasic manner with a terminal $t_{1/2}$ of approximately 1.5 hours. Metreleptin did not appear to extensively distribute outside serum, with a V_{ss} of 83.4 mL/kg. Following s.c. administration, the observed maximal serum levels of 115 ng/mL occurred at 0.875 hours post-dose. Bioavailability of metreleptin in sheep following s.c. administration averaged 59%.

Distribution

Volume of distribution at steady state averaged 179 mL/kg in dog and 154 mL/kg in mouse, which were approximately 3-4 and 3 times the plasma volume in the dog (Study REST070292-P792) and mouse (Study REST070295-OBH.036), respectively, in the single-dose PK study, suggesting that metreleptin distributes to extravascular sites.

The potential placental transfer of recombinant human metreleptin was evaluated in the mouse following single and repeated s.c. administration (Study REST070296-987087). The PK of metreleptin was determined following s.c. administration of 10 mg/kg to Group 1 (single-dose, gestation day [GD] 17), Group 2 (repeated-dose, GD 11-17) and Group 3 (single-dose, non-pregnant).

The results of this study showed that the AUC exposure of pregnant mice was approximately 2 to 3 times greater than those observed in non-pregnant mice after 10 mg/kg s.c. administration of metreleptin. A 4 to 5-fold increase in the $t_{1/2}$ values were also observed in pregnant mice compared to non-pregnant mice.

The C_{max} values in foetal serum and amniotic fluid represented approximately 0.3 to 0.5%, and 0.2 to 0.4%, of the highest concentrations observed in the maternal serum for both Groups 1 and 2, respectively. The AUC values observed in foetal serum and amniotic fluid represented approximately 0.3 to 0.4%, and 0.9 to 1.3%, of those observed in maternal serum for both Groups 1 and 2, respectively.

Metabolism

No formal metabolism studies with metreleptin were submitted, as the product is a recombinant analogue of native human leptin.

Excretion

A study was conducted to investigate the role of the kidneys in the systemic clearance of recombinant metreleptin (Study REST070294-OBH.660). An i.v. dose of 10 mg/kg was administered to three groups of male CD-1 mice. Group 1 consisted of control animals which received no surgical manipulation and no anaesthesia, Group 2 included animals which received a sham-operation, and in Group 3, the animals were bilaterally nephrectomised. Following the i.v. dose, serum concentrations of metreleptin were substantially higher in nephrectomised mice at all time points, compared to control and sham-operated animals. The clearance of metreleptin in Group 3 approximated only 3% of the clearance values in Groups 1 and 2, suggesting that the kidneys were responsible for the majority (>95%) of systemic clearance of metreleptin in mice. There was also a concurrent decrease in the V_{ss} in the nephrectomised animals, suggesting that the kidneys also served as a distribution site for metreleptin.

Pharmacokinetic drug interactions

No PK interaction studies were submitted, but the applicant recognised the potential of metreleptin to alter the formation of cytochrome P450.

Other pharmacokinetic studies

Anti-Drug Antibodies

Serum samples (Days 1, 7, 14, 28, 84, and 168, as well as 1 month recovery) were collected during the course of the 6-month chronic dog toxicity study for the quantitation of metreleptin (Study REST070248-WIL120039). Metreleptin levels appeared to increase upon multiple doses beyond Day 7; however, TK analysis was performed only on samples up to Day 28. Metreleptin levels could not be determined after Day 14 due to interference of the assay by the presence of antibodies. The presence of the antibodies after repeated-dose administration was further evaluated in the chronic dog study, using samples from the 1-month recovery period. Overall, the results indicated that the anti-metreleptin antibodies did not have a neutralising effect on the drug (Study REC-00123). Further evidence suggesting that the anti-metreleptin antibodies were not neutralising was the pronounced PD effects (e.g., body weight loss, and microscopic findings of reduced adipose) recorded in the mouse and dog chronic repeated-dose toxicity studies (studies REST070254-54802 and REST070248-WIL120039, respectively).

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies were submitted.

Repeat dose toxicity

A number of repeat dose toxicity studies were submitted, including 4 studies in mice, 1 in rats, 5 in dogs and 1 in Rhesus monkeys.

The applicant selected, mice and dogs, as the respective rodent and non-rodent species for the metreleptin toxicity program, because the metreleptin pharmacological data indicated that both mice and dogs are biologically responsive to the effects of metreleptin. In addition, the sequence homology of leptin in different animal species is fairly well preserved with 84.9%, 83.6%, 83.6%, 82.2%, and 91.1% sequence homology in mice, rats, rabbits, Beagle dogs, and Rhesus monkeys, respectively, as compared to humans. Finally, results from pharmacokinetic and toxicokinetic (TK) studies in mice and dogs showed that both species have adequate exposure to metreleptin following s.c. injection.

The pivotal studies were the 3/6-month study in Swiss mice and the 1/3/6-month study in Beagle dogs. A summary of the **non-pivotal studies**, is presented in **Table 10.**

Table 10. Summary of the major findings from the non-pivotal, repeat-toxicity studies with metreleptin

Study ID /GLP	Species/ Nr/Sex/Group	Route / dose (mg/kg/day)	Duration	NOAEL (mg/kg)	Major findings
Mouse					
REST070225-54778 REST070226-9811420 REST070227-CK507 /GLP	Mouse (Swiss albino) / 47M/47F (including TK and recovery animals)	s.c. injection / 0, 1, 10, and 100	28 days	1	Several mortalities at 100 mg/kg/day were associated, in part, with overnight food and water deprivation and the severe health status brought on by the PD activity of metreleptin. There was also one mortality in each of the control and 10 mg/kg/day groups. At ≥ 1 mg/kg/day: BW loss, reduced BW gain, and reduced FC, alterations in several clinical chemistry parameters, and fat atrophy; all considered to be exaggerated PD effects. At 10 and 100 mg/kg/day: decreased spleen and thymus weight (with associated histopathology) and other microscopic changes in the stomach and pancreas, were considered related to stress. In the liver, centrilobular hepatocellular degeneration may have been due to hypoxia. At 1 mg/kg/day: PD-related effects were minimal, with no signs of toxicity. Target tissues showed no potential for metreleptin-related cell proliferation.
REST070185-WIL120046 / GLP	Mouse (CD-1) / 25M/25F	i.v. injection / 0, 1, 10, and 100	28 days	10	At 100 mg/kg/day: marked effects, including mortalities (three males and two females) and slight changes in liver enzymes.

					At 10 and 100 mg/kg/day: reductions in BW and FC and associated changes in clinical chemistry, and decreased liver weights. At 1 mg/kg/day: transient reductions in BW and FC. Histopathology: depletion of adipose tissue at all dose levels, and changes at the injection site and in the renal pelvis and/or lower urinary tract at 100 mg/kg/day.
REST070186-WIL120062 / GLP	Mouse (CD-1) / 10M	i.v. injection / 0, 10, 30, 60, 90, and 100	28 day	30	No mortalities. At ≥ 10 mg/kg/day: reductions in BW and FC. At ≥ 30 mg/kg/day: macroscopic evaluation showed depletion of adipose tissue. At ≥ 60 mg/kg/day: microscopic evaluation showed changes in the renal pelvis and/or lower urinary tract.
Rat					
REST070188-WIL120044 /GLP	Rat (Sprague-Dawley) / 6M	s.c. injection / 5	14 days	ND	Decreased BW gains and/or BW, and decreased FC observed in all groups treated with metreleptin (acetate and lyophilized formulations). Slight differences associated with increased drug concentration were apparent in BW effects (decreased) and local injection site effects (non-suppurative inflammation) for both metreleptin formulations.
Dog					
REST070250-	Dog	s.c. injection	14 days	ND	Decreased BW at 0.5 and 1.5 mg/kg/day for both

0437DA31.00 / non-GLP	(Beagle) / 3M	/ 0.15, 0.5, and 1.5			metreleptin and metreleptin 8-site analogue, at 0.15 mg/kg/day metreleptin 8-site analogue, and at 0.5 mg/kg/day metreleptin 6-site analogue. Decreased FC observed throughout the study. Overall, no biological differences were noted between metreleptin and the metreleptin 8- or 6-site analogues at 0.15, 0.5, and 1.5 mg/kg/day.
REST070260-WIL120042 /GLP	Dog (Beagle) / 2M/2F	s.c. injection / 0, 1.5, 3.5, and 5.25	3 weeks	ND	Treatment-related effects included: changes in the clinical condition of the animals, BW loss and/or decreased BW gain, decreased FC, changes in clinical chemistry parameters, and atrophy of adipose tissue. Changes in red blood cell parameters in the high dose (5.25 mg/kg) twice weekly metreleptin and pegylated metreleptin groups, and dark red contents in the stomach and intestine (most likely due to reduced food consumption) and vacuolar changes in the proximal tubules were seen in all pegylated metreleptin groups. Treatment-related effects were typically more pronounced in the animals dosed with pegylated metreleptin, consistent with the prolonged exposure to metreleptin when pegylated. Note: Pegylated metreleptin was used only as a comparative test article in this study, and is not the

					drug for this MAA
REST070203-55026 /GLP	Dog (Beagle) / 3M/3F	s.c. injection, s.c. infusion / 0, 0.5, and 5	28 days	ND	At 0.5 and 5 mg/kg/day by s.c. injection or s.c. infusion: decreased BW and FC, alterations in nutrient metabolism, and decreases in total body fat and lean body mass, all considered to be related to the exaggerated PD effects of metreleptin on fat metabolism. Histopathological changes (e.g., atrophy of mesenteric and perirenal fat) were also regarded as secondary to the PD action of metreleptin.
REST070705-WIL120045 /GLP	Dog (Beagle) / 3M/3F	i.v. injection / 0, 0.5, 1.5, and 5	28 days	5	At ≥ 0.5 mg/kg/day: reduced BW gain and FC, changes in clinical chemistry parameters, reductions in organ weights, and histopathological findings. Gross necropsy findings at 1.5 and 5 mg/kg/day. These effects were considered to be associated with the PD activity of metreleptin, resultant metabolic responses, and generalized nutritional stress. No unique or frank target organ toxicity associated with the i.v. route of administration was apparent.
Monkey					
REST070189-037301 / non-GLP	Monkey (Rhesus) / 1M/2F (Groups 1 and 2); 1F (Group 3)	s.c. injection / 0 and 5	14 days	ND	No mortality, adverse clinical signs or effects on BW or FC. Also no changes in clinical pathology parameters and no significant gross

					observations at necropsy. Histopathology findings primarily consisted of adipose tissue atrophy, and were considered to be related to the PD action of metreleptin.

Pivotal studies

Study REST070254-54802; GLP**:** A 3/6 Month Subcutaneous Toxicity Study of Recombinant-Methionyl Human Leptin (r-metHuLeptin) in Mice Followed by a 28-Day Recovery Period

The objective of this study was to evaluate the potential toxic effects of metreleptin in Swiss albino mice following daily s.c. injection for 3/6 months, and following a recovery period of 28 days. Mice were treated with 0-30 mg/kg doses of metreleptin.

Mortality: prior to the 3-month terminal sacrifice, four animals at 30 mg/kg/day, two at 10 mg/kg/day, and four at 3 mg/kg/day died during the treatment period. One of the animals at 30 mg/kg/day died on Day 33, and the remaining animals died on Day 91, following the overnight food and water deprivation prior to scheduled necropsy. There were no clinical signs observed for one animal dosed at 30 mg/kg/day prior to its recorded death on Day 33. Of the nine animals which were found dead on Day 91, six exhibited pallor, decreased activity, and were cold to touch prior to death; the remaining three animals were found dead prior to the Day 91 clinical examination and had not exhibited any adverse signs on the previous day.

Between Days 91 and the end of the 6-month and recovery periods, several animals of various groups were found dead or were sacrificed in moribund condition. There were no treatment-related clinical observations and the applicant considered that none of the deaths were clearly attributed to treatment

Body weight: Changes from baseline in the percentage of bodyweight at the end of 3 and 6 months of treatment are summarised in **Table 11**.

Table 11. Effect of metreleptin in body weight in the pivotal repeat-dose toxicity in Swiss albino mice, Study REST070254-54802

Dose group (mg/kg)	3 months		6 months		Recovery	
	Male	Female	Male	Female	Male	Female
0	+14	+14	+34	+34	+38	+39
0.3	+13	+10	+29	+28	+36	+35
1	+11	+6	+27	+22	+37	+31
3	+9	+3	+31	+13	+43	+29
10	+6	+1	+28	+14	+39	+35
30	+3	-2	+28	+10	+42	+35

Food consumption: commencing within the first 4 days of treatment, the males and females of the 1, 3, 10, and 30 mg/kg/day groups, and the males of the 0.3 mg/kg/day group, exhibited significantly reduced food consumption **Table 12**.

Table 12. Mean food consumption at different time points in the pivotal repeat-dose toxicity in Swiss albino mice, Study REST070254-54802

Days	control		0.3 mg/kg/d		1 mg/kg/d		3 mg/kg/d		10 mg/kg/d		30 mg/kg/d	
	M	F	M	F	M	F	M	F	M	F	M	F
1-4	18.1	15.4	17.1*	15.1	17.0*	13.5**	16.1**	13.7**	15.7**	13.8**	15.4**	13.1**
11-15	23.0	20.7	22.2	20.5	22.6	20.2	21.7**	19.1##	21.7**	20.0	22.0	19.9
85 - 88	18.6	18.2	18.6	18.8	18.6	18.4	18.0	17.0 ##	18.0	16.6 ###	18.2	16.4 ###
176-179	17.6	17.0	17.0	17.8	16.8	17.8	18.4	16.8	17.3	16.0	17.5	15.3 ##
207-211	11.1	11.8	12.2	12.2	11.7	12.2	12.0	11.9	12.7	12.3	11.7	11.1

* p ≤ 0.05 using Dunnett's test; **p ≤ 0.01 using Dunnett's test; ##p ≤ 0.01 using Dunn's test; ###p ≤ 0.001 using Dunn's test.

Anti-drug antibodies: radioimmunoassay analysis of serum samples indicated the presence of anti-metreleptin antibodies. At 3 months, significant numbers of animals in the dose range of 0.3 to 3 mg/kg/day had seroconverted, and this number appeared to increase after 6 months of dosing. At dose levels of 10 and 30 mg/kg/day, all animals had seroconverted, regardless of the duration of dosing, or after recovery.

Histopathology: microscopically, treatment-related changes were found in the liver, fat, lymphoid organs, stomach, pancreas, and possibly in the injection sites at the end of the 3-month treatment period.. These observations in the liver were not observed in the animals treated for 6 months. At the end of the 3- and 6-month treatment periods, atrophy of mesenteric and/or perirenal fat occurred with a markedly increased incidence and severity in the metreleptin-treated groups as compared to the controls, with a trend towards being more severe at a dose of 30 mg/kg/day.

The NOAEL in this study was determined to be 1 mg/kg/day.

Study REST070248-WIL120039; GLP: A 1/3/6 Month Toxicity and Toxicokinetic Study of Subcutaneously Administered Recombinant Methionyl Human Leptin (r-metHuLeptin) in Beagle Dogs.

The objective of study REST070248-WIL120039 was to evaluate the potential toxic effects of metreleptin in Beagle dogs following daily s.c. injection for 1-, 3-, and 6-month treatment periods, followed by 1-, 4-, and 1-month recovery periods, respectively. Animals were exposed to doses between 0-5 mg/kg/day.

Mortality: one male in the 1.5 mg/kg group was euthanized pre-terminally during Week 8 following a marked body weight loss (greater than that observed for the high dose group males for the same period). During Week 6, one female in the 0.5 mg/kg/day group was euthanized in moribund condition following a marked body weight loss (greater than that observed for the high dose group females for the same period).

Body weight: Changes from baseline in the percentage of bodyweight during the study are summarised in **Table 13.**

Table 13. Change in the percent of baseline (Day 0) body weight (%)in the pivotal repeat-dose toxicity in Beagle dogs, Study REST070254-54802

Week	Control		0.05 mg/kg		0.15 mg/kg		0.5 mg/kg		1.5 mg/kg		5 mg/kg	
	M	F	M	F	M	F	M	F	M	F	M	F
W 4	+9	+4	-7	-2	-5	-8	-13	-16	-21	-22	-30	-28
W 12	+27	+18	+5	+23	+2	-6	+7	-14	-13	-30	-20	-27
W 24	+36	+31	+28	+36	+5	-17	+23	+1	+13	-15	-	-
W 28	+39	+28	-	-	-	-	+9	+6	+13	+2	-	-

Food consumption: The effect of metreleptin on food consumption is summarised in **Table 14**.

Table 14. Mean food consumption at different time points in the pivotal repeat-dose toxicity Beagle dogs, Study REST070254-54802

Weeks	Control		0.05 mg/kg		0.15 mg/kg		0.5 mg/kg		1.5 mg/kg		5 mg/kg	
	M	F	M	F	M	F	M	F	M	F	M	F
0-1	237	200	175*	184	214	149*	193	160	165**	152*	140**	132**
1-2	279	227	158**	176*	184**	142**	147**	120**	106**	115**	79**	79**
3-4	300	244	207**	260	232	206	183**	179*	143**	151**	111**	124**
11-12	318	270	316	315	254	237	305	214	219	132**	204	167
23-24	308	279	323	313	278	171	281	196	222	141*	-	-
27-28	313	267	-	-	-	-	349	263	314	323		

Anti-drug antibody: after 6 months of dosing, an apparent 36% seroconversion was observed in controls, considered to be possibly indicative of misdosing, and this was still largely present after the 1-month recovery phase following the 6-month treatment period (33%). There was a 36% to 100% seroconversion response for the dose groups that received 6 months of dosing. The 5 mg/kg group that was given 3 months of recovery showed only a 25% seroconversion, and no immunoreactivity was detected after 4 months of recovery.

Histopathology: In the first month of treatment, microscopic changes in the gastrointestinal tract, acute haemorrhage in the urinary bladder (observed in two males and one female and graded as mild to severe), lymphoid hyperplasia of the lymph nodes, follicular cell hypertrophy of the thyroid gland for a limited number of animals, and perivasculitis, which affected vessels mainly in the adipose tissue, injection sites, liver, lungs, and heart; perivasculitis also observed in the 0.05, 0.15 and 0.5 mg/kg groups, but limited to adipose tissue in single animals from the 0.05 and 0.15 mg/kg groups, and to the urinary bladder of a single animal in the 0.5 mg/kg group. By the end of the 4-week recovery period, perivasculities was not observed in any of the recovery groups (0.5, 1.5, and 5 mg/kg groups).

At the Week 12 interim necropsy, perivasculitis was limited to the injection site in all groups, including the control group. Even though the incidence and severity grades were greater in the treated groups than in the control group, no dose-relationship was apparent with the exception of somewhat higher severity grades in the 5 mg/kg/day group females. For the 5 mg/kg/day group placed on the second recovery phase (Weeks 12 to 13 through 27 to 28), perivasculitis was not present in the 5 mg/kg/day group at the Week 28 necropsies.

At the Week 24 end of dosing necropsy, perivasculitis was limited to the injection site in all groups, including the control group. Severity grades were greater in the treated groups. For the 0.5 and 1.5 mg/kg/day groups placed on the third recovery phase, perivasculitis at the injection site was seen similarly in the control and treated groups

- **Toxicokinetics**

Study REST070225-54778; GLP : A 28-Day Subcutaneous Toxicity Study of Recombinant-Methionyl Human Leptin (r-metHuLeptin) in Swiss albino mice Followed by a 28-Day Recovery Period

Blood samples were collected from satellite animals on Days 1, 7, 14, and 28. C_{max} and AUC values are only provided for Day 1 and are presented below:

Pharmacokinetic parameter	1 mg/kg	10 mg/kg	100 mg/kg
C_{max} (ng/mL)	367	1,565	37,050
AUC_{0-24h} (ng.hr/mL)	563	6,020	85,000

Following repeated dosing, an increase in serum concentrations was observed for all dose groups on Days 14 and 28. At Day 28 AUCs were increased 3- to 20-fold.

Study REST070248-WIL120039; GLP: A 1/3/6 Month Toxicity and Toxicokinetic Study of Subcutaneously Administered Recombinant Methionyl Human Leptin (r-metHuLeptin) in Beagle Dogs

One animal/sex was used for each day of toxicokinetic analysis.

The following AUC_{0-t} and C_{max} values have been determined:

Table 15. Pharmacokinetic parameters following subcutaneous administration of metreleptin in Beagle dogs, Study REST070248-WIL120039

Day of serum collection	0.05 mg/kg		0.15 mg/kg		0.5 mg/kg		1.5 mg/kg		5 mg/kg	
	M	F	M	F	M	F	M	F	M	F
C_{max} (ng/mL)										
D1	31	24	70	88	291	470	629	939	3,269	2,381
D7	48	32	91	107	302	444	1,027	1,313	3,962	4,059
D14	101	NC	288	358	1,680	2,649	6,700	3,980	NC	7,205
AUC_{0-t} (ng.hr/mL)										
D1	214	238	597	933	3,065	3,407	6,457	6,882	32,335	21,475
D7	251	268	676	772	2,489	2,640	9,982	7,864	32,981	19,076
D14	602	NC	1,767	2,348	18,422	27,482	64,902	37,242	NC	64,817

NC = not calculated

On Day 14, the serum concentration profiles of two animals were not reported because the results from the immunoassay altered with changes in the dilution factors. The serum concentration data on Day 28 were also not determined because the immunoassay was affected by antibody formation in all metreleptin-treated animals.

Interspecies comparison

A summary of safety margins based on exposure at toxicity study NOAELs compared to exposure in adult patients (weight 60 kg) at the MDD of 10 mg is presented in **Table 16.**

Table 16. Metreleptin safety margins from non-clinical toxicity studies

Study Type	Study Number	Species, strain	Route / Duration (weeks)	NOAEL (mg / kg / day) / SAFETY FACTOR	
				mg / kg	mg / $m^{2\dagger}$
Toxicity	REST070225-54778	Mouse, Swiss albino	s.c./4	1/6.0	3/0.48
Toxicity	REST070185-WIL120046	Mouse, CD-1	i.v./4	10/60	30/4.8
Toxicity	REST100056	Mouse, Swiss albino	s.c./4	10/60	30/4.8
Toxicity	REST110184	Mouse, Swiss albino	s.c./4	1/60	30/4.8
Toxicity	REST070186-WIL120062	Mouse, male CD-1	i.v./4	30/180	90/14
Toxicity	REST070254-54802	Mouse, Swiss albino	s.c./28	1/6.0	3/0.48
Toxicity	REST070248-WIL120039	Dog, beagle	s.c./28	1.5/9.0	30/4.8
Reproductive toxicity, Segment 1	REST070257-WIL120049	Mouse, CD-1	s.c./-	30/180	90/14
Reproductive toxicity, Segment 2	REST070258-WIL120060	Mouse, CD-1	s.c./-	30/180	90/14
Reproductive toxicity, Segment 3	REST070259-WIL120068	Mouse, CD-1	s.c./-	30/180; <0.3/1.8	90/14; <0.9/0.1

Genotoxicity

An overview of the studies submitted to evaluate the genotoxicity potential of metreleptin is summarised in **Table 17**.

Table 17. Overview of genotoxicity studies with metreleptin

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
REST070265-G96BX36.502001 Gene mutations in bacteria GLP	Salmonella strains TA98, TA100, TA1535, and TA1537, and E. coli WP2 uvrA	Up to 5,000 µg/plate +/- S9	Negative
REST070282-G96BX36.782 Gene mutations in mammalian cells GLP	CHO-cells, HGPRT-locus	Up to 2,000 µg/mL +/- S9	Negative
REST070283-G96BX36.335001 Chromosomal aberrations in mammalian cells GLP	CHO-cells	Up to 2,000 µg/mL +/- S9	Negative
REST070285-G96BX36.123 Chromosomal aberrations in vivo GLP	Mouse, micronuclei in bone marrow	0, 10, 30, 100 mg/kg	Negative
REST100093 Gene mutations in bacteria GLP	Salmonella strains TA98, TA100, TA1535, and TA1537, and E. coli WP2 uvrA	Up to 5,000 µg/plate +/- S9	Negative
REST110186 Gene mutations in bacteria GLP	Salmonella strains TA98, TA100, TA1535, and TA1537, and E. coli WP2 uvrA	Up to 5,000 µg/plate +/- S9	Negative
REST100094 Chromosomal aberrations in mammalian cells GLP	Human peripheral blood lymphocytes	Up to 5,000 µg/ml +/- S9	Negative
REST110185 Chromosomal aberrations in mammalian cells GLP	Human peripheral blood lymphocytes	Up to 5,000 µg/ml +/- S9	Negative

Carcinogenicity

No carcinogenicity studies with metreleptin were submitted.

Reproduction Toxicity

An overview of the studies submitted to evaluate the reproductive toxicity potential of metreleptin is summarised in **Table 18**.

Table 18. Overview of reproductive toxicity studies with metreleptin

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg &AUC)
REST070257-WIL120049 Male/Female fertility GLP	CD1 mouse 25/sex/dose	0, 1, 10, 30 mg/kg/day SC	M: D-28 for 9 wks F: D-14 - GD 6	**≥1**: ↓BW gain **=30**: ↓food consumption	Fertility: 30 mg/kg/day
REST070298-1901014P Embryo-fœtal development GLP	CD1 mouse 8F/dose	0, 0.3, 1, 3, 10 mg/kg/day SC	GD6-15	F0: **≥1**: ↓BW gain F1: **≥3**: cleft palate	F1: 1 mg/kg/day
REST070258-WIL120060 Embryo-fœtal development GLP	CD1 mouse 25F/dose	0, 1, 10, 30 mg/kg/day SC	GD6-15	F0: **≥1**: ↓BW gain F1: **No effects**	F1: 30 mg/kg/day
REST070267-WIL120059 Embryo-fœtal development GLP	NZW rabbit 5F/dose	0, 0.3, 1, 10, 30 mg/kg/day SC	GD6-20	F0: **No effects** F1: **=30**: 1 foetus with multiple malformations F0: **≥3**: ↓BW gain, food consumption **=30**: ↓BW gain during lactation	F0: 30 mg/kg/day F1: 10 mg/kg/day
REST070259-WIL120068 Peri & postnatal GLP	CD1 mouse 25F/dose	0, 3, 10, and 30 mg/kg/day SC	GD6-LD20	F1: **≥3**: Total litter loss, ↓live litter size, ↓ survival birth-PND4, ↓BW gain up to weaning, delayed vaginal patency **=30**: delayed balanopreputial separation	F1 development: not determined F1 reproduction: 30 mg/kg/day
REST070256-WIL120077 Peri & postnatal GLP	CD1 mouse 25F/dose up to GD18 25F/dose up to LD20	0 and 10 mg/kg/day SC	Vehicle: GD 6-18 Metreleptin: GD 6-15, 15-18, or 6-18	**All groups**: ↓BW gain **GD6-15**: ↑early resorptions **GD6-18**: ↑gestation length, ↓live litter size, ↓survival birth-PND4, ↓growth on PND1	N/A

Local Tolerance

In two non-GLP 14-day studies (studies REST070270-PK96001 and REST070269-P810) in male or female rats using s.c. administration at 5 mg/kg/day, metreleptin was associated with injection-site reactions, the severity (in terms of granulomatous reactions and small crystalloid precipitates) of which was concentration-related. A concentration of 50 mg/mL produced a noticeable reaction (partially reversible) whereas only mild reactions were observed at 5 and 20 mg/mL (which were completely reversible).

In a GLP-compliant single-dose study (study REST070162-CHW6271-125), metreleptin (20 mg/mL [1 mL/site], 5 mg/mL [4 mL/site]) was administered s.c. to male and female rabbits (NZW; 20 mg/mL group, [n = 3/sex]; 5 mg/mL group, [4 males and 2 females]). The injection site was observed for up to 14 days and histopathological evaluations were performed on Days 3 and 14 (n=3/day/dose). At 20 mg/mL, moderate hemorrhage at the injection site and chronic active

inflammation were observed in 1 rabbit on Day 3, but no metreleptin-related changes were observed in other rabbits in the same group and in the 5 mg/mL group.

Other toxicity studies

Antigenicity

Antigenicity was evaluated at metreleptin concentrations of 2.5 and 5 mg/mL in two tests: active systemic anaphylaxis (ASA) and a passive cutaneous anaphylaxis (PCA) using male guinea pigs (Dunkin-Hartley; n = 5 per group) (Study REST070263-CHW6271-123). In the ASA test, s.c. mass/necrosis associated with local inflammatory response was noted at the injection site in animals receiving Freund's Complete Adjuvant (FCA). Severe anaphylaxis occurred in all bovine serum albumin (BSA)- and metreleptin 2.5 and 5 mg/mL-sensitised groups. In the PCA test, the most severe effects occurred in animals treated with BSA and a dose-dependent reaction was observed in the metreleptin groups, augmented by concomitant FCA treatment.

2.3.5. Ecotoxicity / environmental risk assessment

No environmental risk assessment studies were submitted as metreleptin is a protein and therefore unlikely to pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Leptin acts via binding to a cell-surface leptin receptor which is a member of the class I cytokine receptor family, also known as the gp130 receptor family. Metreleptin binding to a chimera Lepr/EPO receptor was measured using a competition binding assay with ^{125}I-leptin (mouse), and IC_{50} values in the range of 0.1-0.3 x 10^{-9} M were recorded. These values are comparable to those published on leptin affinity for its cognate receptor. The bioactivity of human metreleptin has also been shown to be equivalent to human leptin *in vitro* using 32D OBECA cells engineered to contain the human leptin receptor and utilising the OB-R/EPO-R signalling pathway. Even though, distribution including protein binding is likely to be comparable between leptin and metreleptin, it is recommended that the applicant conduct further studies to confirm binding of metreleptin to proteins in serum and to characterise the tissue distribution of metreleptin.

Primary PD studies in leptin deficient mice (*ob/ob*), and rodent models (e.g., genetic, diet and drug-induced) of lipodystrophy demonstrated that ameliorating leptin deficiency by pharmacological administration of metreleptin alleviates many of the metabolic dysregulations associated with the lipodystrophic state. Normal, euleptinemic animals responded to exogenous metreleptin to a lesser degree, and hyper-leptinemic, obese animals exhibited an even lesser response to peripherally administered metreleptin.

A battery of safety pharmacology studies was performed with metreleptin, and results indicated minimal risk for the CNS, cardiovascular, respiratory, renal, and gastrointestinal systems of patients.

No PD drug interaction studies were submitted. However, due to decreased insulin resistance which was seen in many of the non-clinical PD studies, there is an increased risk of hypoglycaemia in patients treated with metreleptin who are on high doses of insulin or insulin secretagogues (e.g., sulfonylureas). A warning is therefore included in the product information on the need to closely monitor blood glucose in such patients and if necessary to reduce the dose by 50% or more of baseline insulin in the first 2 weeks of treatment.

The models used to characterise the PK profile of metreleptin (mice, dogs, and sheep) were considered acceptable. The models used of The studies in mice included normal, bilaterally nephrectomised, and pregnant animals, and examined the PK profiles of metreleptin following s.c. or intravenous (i.v.) administration. The PK profile of metreleptin was evaluated in dogs following s.c. and i.v. administration and in sheep following s.c. or i.v. injection. Limited toxicokinetic (TK) analyses were also conducted in GLP toxicity studies in mice and dogs.

In mouse PK studies, the bioavailability of subcutaneously administered metreleptin was determined to be approximately 82%. Following s.c. dosing, T_{max} in mice ranged from approximately 10 to 30 min., whereas T_{max} ranged from approximately 3 to 4 hours in dogs. In both mice and dogs, there was no gender-related difference in the PK of metreleptin. Also in both species, metreleptin exposure tended to increase over time following repeated s.c. dosing. At the same time, serum reactivity ratio, indicative of an antibody-response against metreleptin, increased after repeated s.c. administration. The time-course of antibody formation appeared to coincide with increased exposure – presumably related to decreased renal filtration of the antibody complex.

Volume of distribution at steady state averaged were approximately 3-4 and 3 times the plasma volume in the dog and mouse, respectively, in the single-dose PK study, suggesting that metreleptin distributes to extravascular sites. AUC exposure of pregnant mice was approximately 2 to 3 times greater than those observed in non-pregnant mice after 10 mg/kg s.c. administration of metreleptin. A 4 to 5-fold increase in the $t_{1/2}$ values were also observed in pregnant mice compared to non-pregnant mice. The higher metreleptin exposure and longer $t_{1/2}$ observed in the pregnant animals may be related to a reduced elimination capacity by binding to soluble leptin receptor found at higher levels in pregnant mice.

While metreleptin reached the foetal serum and amniotic fluid through placental transfer, the exposure of the foetus to metreleptin was minimal (less than 1%).

No formal metabolism studies have been conducted with metreleptin, and were not considered to be necessary since metreleptin is a recombinant analogue of native human leptin, differing from the native molecule by a single methionyl group at the N-terminus end.

The majority (>95%) of systemic clearance of metreleptin in mice occurs through the kidneys. There was also a decrease in the Vss in the nephrectomised animals, suggesting that the kidneys also serve as a distribution site for metreleptin. It is possible therefore that the pharmacokinetics may be altered in subjects with renal impairment.

No formal non-clinical PK interaction studies were performed. It is known however, that leptin is a cytokine with the potential to alter the formation of cytochrome P450. Therefore, a recommendation in the product information, that when starting or stopping therapy with metreleptin, patients taking medicinal products which are individually adjusted and metabolised via CYP450 (e.g., theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin) should be monitored as doses may need to be altered to maintain therapeutic effect, is considered necessary.

Metreleptin levels could not be determined after Day 14 due to interference of the assay by the presence of antibodies. Overall, the results indicated that the anti-metreleptin antibodies did not have a neutralising effect on the drug. Further evidence suggesting that the anti-metreleptin antibodies were not neutralising was the pronounced PD effects (e.g., body weight loss, and microscopic findings of reduced adipose) recorded in the mouse and dog chronic repeated-dose toxicity studies.

Pivotal repeated dose toxicity studies have comprise two 6-month studies with daily s.c. administration of metreleptin: one in Swiss mice, including a recovery period and an interim sacrifice at 3 months, and another in Beagle dogs, with interim sacrifices at 1 and 3 months of treatment and three recovery periods (after 1, 3 and 6 months of treatment).

Effects most consistently observed and attributed to the pharmacological effect included a reduction in body weight or body weight gain, decreased food consumption and atrophy of adipose tissue. Other effects observed were also generally considered as primarily or secondarily related to the intended activity of metreleptin, or to stress. Deaths which have occurred during the studies and for which a cause has been ascribed in relation to metreleptin have been attributed to overnight food and water deprivation prior to necropsy (mice) or marked body weight loss (dogs). Development of anti-drug antibodies was also observed in both studies.

The liver seems to be a target organ in both species as well. However, no indication of liver toxicity was seen in the clinical trials, and therefore this is likely not clinically relevant. In CD1 mice, the kidney was also identified as target organ. Tubular degeneration, pyelitis and pelvic deposits were the main findings at doses of 60 mg/kg/day iv dosing or higher. No toxicokinetics were performed in these studies with CD1 mice, but it can be assumed that exposure was sufficiently in excess of the human exposure at the maximum dose, based on other mouse data. A safety margin of 5 is expected at the NOAEL for the kidney which was not identified as a target organ in the clinical trials.

Bioanalytical determination of toxicokinetics exposure in the studies, where available, correlated with reproducible dose-related effects on pharmacodynamics and toxicology, although there were issues with TK assay interference by antibodies in the dog following repeat treatment. However, formation of antibodies did not impact on pharmacodynamics and toxicology in this species. However, as the validation reports of the methods used were not submitted it is recommended that the applicant should supply these following the authorisation of the product.

The applicant did not conduct any carcinogenicity studies with metreleptin. This was acceptable based on the fact that the pharmacological profile of metreleptin is essentially identical to that of endogenous leptin. Furthermore, metreleptin was shown to be devoid of genotoxic potential and pre-neoplastic, proliferative lesions were not reported in chronic subcutaneous toxicity studies in mice and dogs.

Studies to investigate effects on reproductive toxicity were conducted in CD-1 mice and NZW rabbit. No effects on fertility and early embryonic development were observed. Reproductive toxicity studies conducted in mice did not reveal any adverse effects on mating, fertility or embryo-foetal development up to the maximum tested dose, approximately, 15-fold the maximum recommended clinical dose, based on body surface area of a 60 kg patient.

In a pre- and postnatal development study in mice, metreleptin caused prolonged gestation and dystocia at all tested doses, starting at, approximately, a dose identical to the maximum recommended clinical dose, based on body surface area of a 60 kg patient. Prolonged gestation resulted in the death of some females during parturition and lower survival of offspring within the immediate postnatal period. These findings were considered to be related indirectly to metreleptin pharmacology, resulting in nutritional deprivation of treated animals, and also possibly, due to an inhibitory effect on spontaneous and oxytocin-induced contractions, as has been observed in strips of human myometrium exposed to leptin. Decreased maternal body weight was observed from gestation throughout lactation at all doses and resulted in reduced weight of offspring at birth, which persisted into adulthood. However, no developmental abnormalities were observed and reproductive performance of the first or second generations was not affected at any dose.

The study did not include toxicokinetics analysis. Nevertheless, the occurrence of reductions in body weight/ body weight gain and food consumption, among the parental generation, together with the read across from a separate pharmacokinetic study in pregnant mice (Study REST070296-987087), indicates that metreleptin has been tested at sufficiently high doses.

Local tolerance reactions were observed when rabbits were injected with a metreleptin concentration of 50 mg/ml, which persisted after a 2 week recovery period. Although no signs of irritation were

evident, at 20 mg/ml one animal had chronic active inflammation at the injection site. Concentrations of 5 mg/ml, which are closer to the dose intended for human use, showed no signs of skin irritation or any other local effect.

In antigenicity studies, metreleptin was shown to have the potential to induce active systemic anaphylaxis and passive cutaneous anaphylaxis in guinea pigs, in which metreleptin is a foreign protein. However, the clinical relevance of this finding is unlikely, since most foreign proteins can elicit similar responses

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. No environmental risk assessment studies were submitted which is in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2).

2.3.7. Conclusion on the non-clinical aspects

Metreleptin has been adequately characterised in non-clinical pharmacology, pharmacokinetic and toxicology studies. Nevertheless it is recommended that the applicant submits the validation reports for the methods used in the pivotal toxicity studies (with TK and immunogenicity) in mouse and dog and further characterises binding of metreleptin to proteins in serum as well as its tissue distribution.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

STUDY ID START DATE END DATE	LOCATION (NO. OF CTRS)	STUDY OBJECTIVES	STUDY DESIGN	STUDY DRUG AND CONTROL DOSE, ROUTE OF ADMINISTRATION, REGIMEN, DURATION OF TREATMENT	TOTAL ENROLMENT: (METRELEPTIN/ CONTROL)
NIH Study 991265/ 20010769 *24 JUL 2000* *19 DEC 2014*	US[a] (1)	Efficacy, Safety	Open-label, Investigator-sponsored 991265: Pilot study 20010769: Long-term study	991265 Predicted target dose of metreleptin to achieve normal leptin concentration (100%) was: 0.03 mg/kg (females) and 0.04 mg/kg (males) SC BID Dose escalation scheme: Month 1: 50% of predicted dose Month 2: 100% of predicted dose Month 3 through EOS: 200% of predicted dose or maximum tolerated dose Up to 8 months 20010769 100% target dose of metreleptin was modified to: 0.08 mg/kg/day (females >10 years), 0.06 mg/kg/day (females 6 months to 9 years), and 0.06 mg/kg (males) QD, SC Continue until specific discontinuation criteria related to toxicity, lack of efficacy or compliance were met Up to 14 years	Total: 107/0 GL: 66/0 PL: 41/0 PL subgroup[b]:31/0
FHA101 (MB002002) 30 MAR 2009 10 JAN 2015	US (6)	Efficacy, Safety, Tolerability. PK	Open label	For patients weighing ≤ 40 kg: Metreleptin 0.06 mg/kg QD SC For patients weighing > 40 kg: Males: Metreleptin 2.5 mg QD SC Females: Metreleptin 5.0 mg QD SC Based on response, dose adjustments permitted in increments or decrements of 0.02 mg/kg for patients ≤40 kg and 1.25 to 2.5 mg for patients >40 kg. Up to 5.5 years	Total: 41/0 GL: 9/0 PL: 32/0 PL subgroup[b]: 7/0

Abbreviations: BID = twice daily;; F = female; GL = generalised lipodystrophy; HbA1c = glycosylated haemoglobin-specific A1c fraction; IND = Investigational New Drug; M = male; NIH = National Institute of Health; PL = partial lipodystrophy; QD = once daily; SC = subcutaneous; US = United States;

[a] *The study was conducted at the NIH in the US; however, patients from outside the US were enrolled.*

[b] *PL patients with baseline HbA1c ≥6.5% and/or triglycerides ≥2.26 mmol/L and, in Study FHA101, with baseline leptin <12 ng/mL*

2.4.2. Pharmacokinetics

Metreleptin PK has been quantified in 2 clinical studies in healthy subjects across a broad range of BMIs (normal weight to obese) as part of the Amgen obesity clinical development programme (LEPT-970121 and LEPT-950272). Study LEPT-970121 investigated a dose range of 0.3 to 3.0 mg/kg/day via intravenous (IV) bolus injection, and Study LEPT-950272 investigated a dose range of 0.01 to 0.3 mg/kg/day via subcutaneous (SC) bolus injection.

A further 2 clinical studies in overweight/obese subjects (DFA101 and DFA103) were also conducted as part of the Amgen obesity clinical development program. These studies were combination studies with a second investigational agent (pramlintide) and are therefore not directly relevant to this application. However, PK data from these studies were included in comparative PK/PD analysis (REST120204) along with data from Studies FHA101 and LEPT-950272.

Absorption

Study LEPT-950272

This was a randomised, double-blind, placebo-controlled, multiple ascending dose study of SC metreleptin in healthy subjects across a range of doses.

The PK profile of metreleptin after a single SC dose was characterised by an absorption phase leading to peak concentrations at approximately 4 hours, followed by a mono-exponential elimination phase associated with a half-life of approximately 3 to 5 hours **Table 19**.

Table 19. PK parameters of metreleptin on day 1 after a SC bolus injection- Study LEPT-950272

PK PARAMETER[a]	METRELEPTIN SC BOLUS DOSE				
	0.01 mg/kg	0.03 mg/kg	0.1 mg/kg	0.3 mg/kg (5 mg/mL)	0.3 mg/kg (20 mg/mL)
	N=16	N=16	N=31	N=26	N=7
T_{max} (h)	3.0 (2.0, 18.0)	3.0 (3.0, 6.0)	4.0 (2.0, 8.0)	4.0 (2.0, 8.0)	4.0 (3.0, 8.0)
C_{max} (ng/mL)	13.6 (73)	37.2 (46)	119.2 (27)	342.5 (30)	207.0 (20)
nC_{max} (ng/mL/mg/kg)[b]	1360 (73)	3720 (46)	1192 (27)	1142 (30)	690 (20)
$t_{½}$ (h)	4.67 (64)	4.65 (42)	4.33 (63)	3.78 (36)	3.12 (22)
$AUC_{0-\infty}$ (ng•h/mL)	131.0 (80)	336.5 (39)	1180.0 (23)	3656.9 (21)	2059.4 (25)
$AUC_{0-\infty}$/D (ng•h/mL/mg/kg)	13099 (80)	11218 (39)	11800 (23)	12190 (21)	6865 (25)
CL/F (mL/kg/h)	136.8 (82)	106.2 (50)	89.0 (23)	85.6 (21)	152.6 (22)
V_z/F (mL/kg)	803.8 (79)	714.8 (63)	519.3 (53)	444.4 (26)	673.8 (22)

Abbreviations: $AUC_{0-\infty}$=Area under the concentration-time curve from time zero extrapolated to infinity, $AUC_{0-\infty}$/D=dose-normalised $AUC_{0-\infty}$, CL=total body clearance, C_{max}=maximum concentration, NA = not applicable, nC_{max}=dose-normalised C_{max}, SC=subcutaneous, CV% = percent coefficient of variation, t½ =terminal half-life; Vz=volume of distribution

[a] Values are presented as mean (CV%) except for T_{max} which is presented as median (minimum, maximum)

[b] Derived from the values in this table.

Study LEPT-970121

Study LEPT-970121 was a randomised, double-blind, placebo-controlled multiple ascending dose study of metreleptin in healthy adult subjects. Metreleptin was administered once daily intravenously (bolus at an approximate rate of 1 mL/min).

In total, 125 subjects (83 male, 42 female) between the age of 19 and 65 years were randomised: 83 to metreleptin and 42 to placebo. 111 subjects completed the study and were included in PK analyses **Table 20.**

Table 20. Metreleptin Pharmacokinetic Parameters after IV Metreleptin Administration Study LEPT-970121

PK PARAMETERS[a]	METRELEPTIN IV DOSE				
	0.1 mg/kg GD	0.3 mg/kg GD	0.3 mg/kg FD	1.0 mg/kg FD	3.0 mg/kg FD
Day 1,					
N	N=6	N=9	N=27	N=14	N=12
C_{max} (ng/mL)	2128.5 (20)	5858.8 (22)	6160.0 (23)	17582.0 (17)	32887.3 (15)
nC_{max} (ng/mL/mg/kg)	21284.9 (20)	19529.4 (22)	20533.4 (23)	17582.0 (17)	10962.4 (15)
$t_{½}$ (h)	2.97 (53)	3.78 (47)	3.34 (56)	3.41 (25)	3.42 (24)
$AUC_{0-\infty}$ (ng•h/mL)	1360.8 (21)	3905.1 (23)	3908.8 (19)	12544.7 (20)	32775.7 (22)
$AUC_{0-\infty}/D$ (ng•h/mL/mg/kg)	13607.7 (21)	13017.2 (23)	13029.2 (19)	12544.7 (20)	10925.2 (22)
CL (mL/h/kg)	76.6 (24)	79.9 (19)	79.6 (20)	82.5 (19)	95.8 (23)
V_z (mL/kg)	331 (61)	433 (55)	370 (50)	398 (23)	463 (25)
Day 15[b]					
N	NA	NA	N=29	N=13	N=12
C_{max} (ng/mL)	NA	NA	5533.0 (28)	16367.4 (18)	32055.5 (15)
nC_{max} (ng/mL/mg/kg)	NA	NA	18443.4 (28)	16367.4 (18)	10685.2 (15)
$R_{ac,Cmax}$	NA	NA	0.9 (26)	0.9 (11)	1.0 (13)

Abbreviations: $AUC_{0-\infty}$=Area under the concentration-time curve from time zero extrapolated to infinity, $AUC_{0-\infty}/D$=dose-normalised $AUC_{0-\infty}$, CL=total body clearance, C_{max}=maximum concentration, IV=intravenous, NA=not applicable, nC_{max}=dose-normalised C_{max}, CV%=percent coefficient of variation, FD=fixed dose, GD=graduated dose, $R_{ac,Cmax}$=accumulation ratio (Day 15/Day1), t½=terminal half-life; Vz=volume of distribution

[a] Values are presented as mean (CV%).

[b] Given the limited sampling duration on Day 15, $t_{1/2}$, $AUC_{0-\infty}$, CL and Vz have not been reported.

By comparing the $AUC_{0-\infty}$ values from SC dosing to IV dosing, the absolute bioavailability of SC metreleptin at 0.3 mg/kg was estimated to be approximately 94%. Half-life values were similar after SC and IV dosing. CL/F and Vz/F were also similar to CL and Vz, respectively (i.e., after SC and IV dosing) at 0.3 mg/kg

No clinical studies have been conducted to formally evaluate the PK disposition of metreleptin in LD patients. Metreleptin PK data after SC administration in LD patients are available from a small subset of patients in Study FHA101 (13 patients with 8 to 10 hour PK profile.

Metreleptin was administered SC in LD patients in study FHA101. PK parameters were only calculated for the metreleptin naïve patients on day 1 and are presented in **Table 21** together with the results from overweight/obese subjects

Table 21. Metreleptin PK parameters (baseline adjusted and dose normalised) for LD patients (Study FHA101) and Normal, Overweight and Obese Subjects (Amgen Study LEPT-950272, and Amylin Studies DFA101 and DFA103) after a single SC dose on day 1

Parameter	Lipodystrophy Patients (FHA101)	Subjects with a Range of BMI Values (LEPT-950272)	Overweight/Obese Subjects (DFA101)	Overweight/Obese Subjects (DFA103)
$AUC_{0\text{-}10h}$ (h·ng/mL/kg)				
n	5	89	9	27
Mean (SD)	58.55 (32.564)	82.17 (33.664)	90.97 (34.988)	72.75 (20.698)
Geometric Mean	51.89	75.02	84.86	69.71
CV%	55.62	40.97	38.46	28.45
Median	48.30	78.97	84.42	73.73
Min, Max	27.9, 107.9	19.0, 208.0	47.5, 147.0	32.5, 116.6
25th, 75th Percentile	35.3, 73.5	57.5, 108.8	63.1, 120.2	56.5, 89.2
10th, 90th Percentile	27.9, 107.9	44.8, 121.4	47.5, 147.0	41.2, 100.0
C_{max} (ng/mL/kg)				
n	5	89	9	27
Mean (SD)	9.02 (5.555)	15.30 (7.320)	13.33 (6.414)	9.55 (2.690)
Geometric Mean	7.84	13.76	11.97	9.16
CV%	61.60	47.83	48.12	28.17
Median	6.88	13.43	10.72	9.76
Min, Max	4.3, 17.8	4.0, 39.7	6.6, 22.9	4.5, 14.2
25th, 75th Percentile	5.1, 10.9	10.2, 18.9	8.2, 18.6	7.2, 12.2
10th, 90th Percentile	4.3, 17.8	7.7, 24.8	6.6, 22.9	6.5, 13.1
T_{max} (h)				
n	5	89	9	27
Median	4.00	4.00	6.00	4.00
Min, Max	2.0, 6.0	2.0, 8.0	4.0, 10.0	2.0, 10.0
25th, 75th Percentile	3.0, 6.0	3.0, 4.0	4.0, 10.0	3.0, 8.0
10th, 90th Percentile	2.0, 6.0	3.0, 6.0	4.0, 10.0	3.0, 10.0

Additional information is available from a study in 7 Japanese patients with general LD described in literature (Ebihara, 2007 J. Clin. Endocrinol. Metab.). These patients received metreleptin BID for the first year, followed by transition to QD dosing after 1 year of treatment. The 100% replacement dose of metreleptin was 0.02 mg/kg/day for men, 0.03 mg/kg/day for females under 18 years of age, and 0.04 mg/kg/day for adult females. The peak plasma leptin levels occurred at approximately 2 hours after the metreleptin dose. Mean (standard error [SE]) C_{max} plasma leptin levels were 4.05 (0.19), 9.80 (1.70), 18.95 (1.58), and 34.48 (2.11) ng/mL for 50, 100, 200, and 400% target doses, respectively. However, information is not available from this publication regarding PK sampling times.

Intra- and inter-individual variability

In Study LEPT-970121, metreleptin PK variability was low with percent coefficients of variation for C_{max} and $AUC_{0\text{-}\infty}$ of 15 to 28%. In study LEPT-950272, variability in metreleptin PK was high at the lower doses with CV% for C_{max} and $AUC_{0\text{-}\infty}$ being 40 to 80% after bolus doses of 0.01 and 0.03 mg/kg, although variability was lower at the higher doses with CV% of 21 to 30% at 0.1 and 0.3 mg/kg.

Variability in dose-normalised AUC_{0-10h} and C_{max} across studies (REST120204) was higher in LD patients compared to healthy/obese subjects with CV% for AUC_{0-10h} and C_{max} of respectively 55.6 and 61.6% in LD patients and a maximum CV% for AUC_{0-10h} and C_{max} of respectively 40.97 and 48.12% in healthy subjects.

Distribution

The mean volume of distribution (Vz ± SD) following IV dosing in healthy adult subjects was 370 ± 184 mL/kg, 398 ± 92 mL/kg, and 463 ± 116 mL/kg for 0.3, 1.0 and 3.0 mg/kg/day doses, respectively. The volume of distribution on Day 15 following multiple IV injections was 186, 263 and 275 mL/kg, respectively for the 0.3, 1.0 and 3.0 mg/kg/day (**Table 20**).

Elimination

Metreleptin is an analogue of human leptin which is believed to be predominantly renally eliminated in humans. Nonclinical data suggest renal clearance is the major route of metreleptin elimination, with no apparent contribution of systemic metabolism or degradation (study REST070294-OBH.660).

Following IV dosing, serum leptin concentrations declined mono-exponentially with a half-life of 3.3 h to 3.4 h on Day 1 across all doses (0.3-3.0 mg/kg/day) and a total body clearance (CL) of 80.0 to 96.0 mL/kg/h.

The half-life of metreleptin following a single SC bolus dose of 0.01 to 0.3 mg/kg in healthy subjects was reported to be approximately 3 to 5 hours. CL/F ranged from 86 to 137 mL/h/kg.

Dose proportionality and time dependencies

- **Dose proportionality**

Results of study LEPT-970121 showed that metreleptin exposure (C_{max} and $AUC_{0-\infty}$) increased approximately proportionally to dose after single intravenous injection from 0.1 to 1.0 mg/kg. A less than dose-proportional increase in C_{max} and $AUC_{0-\infty}$ values was seen with the highest dose group (3.0 mg/kg/day). Clearance was independent of dose across the range 0.1 to 1.0 mg/kg, although it was higher at 3.0 mg/kg. After multiple IV injections (day 15), results were similar for C_{max} (approx. dose proportional for 0.3 and 1.0 mg/kg/day). However, no conclusions could be drawn for $AUC_{0-\infty}$ since these values could not be estimated confidently due to limited sampling duration.

In study LEPT-950272, a close to dose-proportional increase in C_{max} concentrations and AUC values was seen in subjects who received a single dose of metreleptin (5 mg/mL) via SC bolus injection across a dose range from 0.01 to 0.3 mg/kg . The $t_{1/2}$ values and the dose-normalised $AUC_{0-\infty}$ values among the different dosing regimens were similar (data not shown).

- **Time dependency**

Healthy subjects

After once daily IV metreleptin administration in study LEPT-970121, the mean Day 15 to Day 1 metreleptin C_{max} ratios were 0.9, 0.9 and 1.0 for 0.3, 1.0 and 3.0 mg/kg/day, respectively. An increase in exposure over time was reported in studies LEPT-970121 and LEPT-950272 in subjects who developed anti-metreleptin antibodies.

LD patients

Fasting serum leptin concentrations (endogenous leptin and metreleptin) from baseline to month 12 were reported in study NIH991265/20010769 and in study FHA101 (both in LD patients). An increase in leptin concentrations were noted by month 3 (FHA101) or month 4 (NIH991265/20010769) with a further increase to month 6 (both studies) with leptin concentrations levelling off after that time.

The results for study FHA101 are presented in Figure 4. In GL patients, mean increases from baseline in leptin concentrations were 0.1 ng/mL at Month 3 (n=3) and 56.5 ng/mL at Month 6 (n=2). Changes from baseline in leptin concentration in the PL subgroup were greater than those in the overall GL group; mean increases were 101.1 ng/mL at Month 3 (n=4), 502.8 ng/mL at Month 6 (n=4), 650.5 ng/mL at Month 12 (n=4).

In study NIH991265/20010769, mean increases from baseline in leptin concentrations at Months 4, 6 and 12 were 20.1, 75.0 and 49.7ng/mL, respectively in GL patients. Results for changes from baseline in leptin concentration in the PL subgroup were similar to the overall GL group; mean increases at Month 4, 6 and 12 were 16.9, 124.5 and 43.1 ng/mL, respectively.

Special populations

No formal studies have been conducted to specifically evaluate the PK of metreleptin in special populations, however where possible, the effects of different intrinsic factors on the PK was assessed within and across studies.

A covariate analysis was performed in REST120204 using data from study FHA101 (lipodystrophy program) and Studies LEPT-950272, DFA101, and DFA103 (Amgen Obesity program).

- **Impaired renal function**

The relationship between metreleptin PK and baseline demographic parameters (including estimated GFR (eGFR)) was explored using data from studies FHA101, LEPT-950272, DFA101, and DFA103. This analysis showed an inverse relationship between mean C_{max} and $AUC_{0\text{-}10h}$ values with renal function (data not shown).

In order to supplement the limited PK data, the applicant submitted a pharmacodynamic (PD) analysis according to baseline creatinine clearance for study NIH 991265/20010769 **Table 22.**

A similar analysis was conducted in the FHA101 study which showed that the dose in the renally impaired group was actually higher (0.10 mg/kg) than the dose in the renal ‘normal’ group (0.06 mg/kg).

Table 22: Analysis of the Primary Efficacy Endpoints using LOCF by Baseline Creatinine Clearance Subgroup (< 150.93 mL/min: upper table; ≥150.93 mL/min: lower table). Median Total Daily Dose: 0.09 mg/kg. Excluding Patient 901-080: NIH 991265/20010769 (Full Analysis Set)

	Generalised Lipodystrophy			Partial Lipodystrophy	
Parameter Statistic	Males	Females	Overall	Severe Phenotype	Overall
Change from baseline in HBA1c to Month 12					
n	5	16	21	15	22
Mean (SD)	-1.3 (0.72)	-1.5 (1.71)	-1.4 (1.52)	-0.7 (0.88)	-0.4 (0.95)
[95% CI]	[-2.2, -0.4]	[-2.4, -0.6]	[-2.1, -0.7]	[-1.2, -0.3]	[-0.8, 0.0]
p-value[a]	0.016	0.004	<0.001	0.006	0.069
% Change from baseline in Triglycerides to Month 12					
n	5	16	21	15	22
Mean (SD)	-23.5 (34.24)	-31.7 (58.31)	-29.8 (52.89)	-31.9 (31.43)	-16.1 (47.45)
[95% CI]	[-66.1, 19.0]	[-62.8, -0.7]	[-53.9, -5.7]	[-49.3, -14.5]	[-37.1, 5.0]
p-value[a]	0.199	0.046	0.018	0.002	0.127

Abbreviations: CI = confidence interval; LOCF = last observation carried forward; max = maximum; min = minimum; SD = standard deviation
[a] P-values computed using paired t-tests.
Note: The LOCF imputation method only takes into account results that are at least 6 months (180 days) post-baseline.
Note: Creatinine Clearance estimated using the Cockcroft-Gault formula.

	Generalised Lipodystrophy			Partial Lipodystrophy	
Parameter Statistic	Males	Females	Overall	Severe Phenotype	Overall
Change from baseline in HBA1c to Month 12					
n	9	29	38	12	14
Mean (SD)	-2.2 (2.89)	-2.7 (2.21)	-2.6 (2.35)	-1.2 (1.58)	-1.0 (1.54)
[95% CI]	[-4.4, 0.1]	[-3.5, -1.8]	[-3.3, -1.8]	[-2.2, -0.2]	[-1.9, -0.1]
p-value[a]	0.055	<0.001	<0.001	0.028	0.035
% Change from baseline in Triglycerides to Month 12					
n	9	27	36	12	14
Mean (SD)	-33.3 (46.91)	-33.5 (90.04)	-33.5 (80.78)	-44.3 (29.89)	-28.3 (49.50)
[95% CI]	[-69.4, 2.8]	[-69.1, 2.1]	[-60.8, -6.1]	[-63.3, -25.3]	[-56.9, 0.3]
p-value[a]	0.066	0.064	0.018	<0.001	0.052

- **Impaired hepatic function**

As metreleptin is cleared primarily by the kidney, hepatic dysfunction is not expected to affect serum concentrations of metreleptin.

- **Gender**

Using an ANCOVA analysis, no effects of sex on metreleptin PK parameters were noted following IV dosing (Studies LEPT-970121). Following SC dosing (LEPT-950272), sex had a statistically significant effect on dose-normalised C_{max} and AUC, which were higher in females than males.

- **Race**

No formal studies have been conducted to evaluate the effect of race on the PK of metreleptin.

- **Weight**

An analysis of covariance to test the effects of BMI on dose-normalised AUC_{0-24h}, dose-normalised C_{max} and CL/F of subjects who received metreleptin via a single SC bolus injection (LEPT-950272) showed that BMI had a statistically significant effect on dose-normalised AUC_{0-24h} (higher in subjects with a higher BMI) and on CL/F (increasing with decreasing BMI). After a single IV metreleptin dose, BMI was tested to have statistically significant effects on C_{avg}, dose-normalised C_{max}, $t_{1/2}$, dose-normalised $AUC_{0-\infty}$, and CL values. However, such BMI effects were not observed after multiple dose (Day 15) administration of metreleptin (LEPT-970121).

A comparative analysis of PK data from healthy subjects and lipodystrophy patients noted an inverse relationship between the mean C_{max} for metreleptin and baseline BMI, although there was no apparent relationship between AUC and baseline BMI.

- **Elderly**

In Studies LEPT-970121 and LEPT-950272, ANCOVAs were performed to test the effect of age on metreleptin PK parameters in healthy subjects. Following IV dosing, age had a statistically significant effect on average concentrations (C_{avg}), $AUC_{0-\infty}$/D and CL with older subjects tending to have higher C_{avg} and $AUC_{0-\infty}$/D and lower CL than younger subjects. Following SC dosing, no effects of age were noted.

- **Children**

In Study NIH 991265/20010769, changes over time in fasting serum leptin concentrations were generally consistent for patients aged ≥6 to <12 years, ≥12 to <18 years and ≥18 years of age; the sample for patients <6 years was small (5 patients with a variable number of leptin sampling points) but also appeared to be consistent with the overall results.

Likewise, in Study FHA101, changes over time in serum leptin concentrations were generally consistent for patients aged ≥6 to <12 years (n=2) and ≥12 to <18 years (n=1) in the GL group. In the PL subgroup, none of the patients were aged <18 years.

Pharmacokinetic interaction studies

Because metreleptin is believed to be predominantly renally cleared, the applicant did not submit *in vitro* studies with human biomaterials such as human liver microsomes / cytochrome P450 expressing cell lines to. In addition, no formal clinical studies have been conducted to evaluate drug-drug interactions with metreleptin.

Immunogenicity

Three different assays for the detection of anti-drug antibodies (ADAs) have been used throughout the clinical development programme for metreleptin.

A Radioimmunoassay (RIA) was initially developed to detect the presence of ADAs to metreleptin in plasma specimens from PK studies LEPT-970121 and LEPT-950272; safety studies in obese subjects LEPT-970213, LEPT-970164, LEPT-980236, LEPT-970171, and LEPT-970188).

During the conduct of LEPT-980236, a validated biosensor immunoassay became available and replaced the RIA used for the analysis of samples corresponding to earlier time points in this study. A biosensor assay (using a different sensor chip) was also used to detect ADAs in LD patients in study NIH 991265/2001769.

Measurement of binding antibodies to metreleptin in LD patients in Study FHA101 and study NIH 991265/2001769 was performed using a electrochemiluminescence (ECL) bridging-format assay. This method was also used for detection of the binding antibodies in the pramlintide/metreleptin combination obesity studies.

Samples that were positive for antibodies to metreleptin for any of the ADA testing methodologies (RIA, biosensor and ECL assays) were tested in a cell-based bioassay to evaluate for neutralising activity. For NIH study 991265/2001769, all samples assessed for neutralising activity were assayed in parallel to the binding antibody testing.

In both obese subjects and LD patients, a high incidence of development of ADAs to metreleptin was reported. In patients with LD receiving metreleptin with available ADA data, 88% had a positive ADA response, whereas 85% of patients included in the 5 Phase 2 Amgen obesity studies had at least 1 post-baseline positive ADA response (and a negative antibody titer at baseline).

Impact of ADAs on pharmacokinetics

Healthy (normal to obese) subjects

In LEPT-970121, following multiple dosing of metreleptin administered IV in normal and obese subjects at doses ranging from 0.3, 1.0 and 3.0 mg/kg/day, exposure (Day 15 to Day 1 metreleptin AUC ratios) was increased in subjects with a positive antibody to metreleptin post baseline, compared with subjects who did not develop antibodies to metreleptin (ANCOVA analysis). Similarly in LEPT-950272, subjects who tested negative for antibody formation did not show accumulation from Day 1 to Day 28. In subjects who tested positive for antibody formation, higher metreleptin concentrations were observed on Day 28 as compared with Day 1 and Day 14 results.

LD patients

A comparison of the 8 to 10 hour PK profiles conducted 3 months apart (PK1 and PK2) in 13 patients in study FHA101 revealed that although the overall shape of the profiles remained the same, higher metreleptin exposure (dose-normalised) was observed in the presence of high ADA titres of to metreleptin.

The impact of immunogenicity on metreleptin PK in patients with lipodystrophy in the NIH pivotal study has not been formally evaluated due to the limited antibody and leptin level data.

2.4.3. Pharmacodynamics

No human PD studies were submitted.

Mechanism of action

Metreleptin exerts its function by binding to and activating the human leptin receptor (ObR), which belongs to the Class I cytokine family of receptors that signals through the JAK/STAT transduction pathway.

2.4.4. Discussion on clinical pharmacology

Metreleptin PK has been quantified in 2 clinical studies (LEPT-970121 and LEPT-950272) in healthy subjects across a broad range of BMIs (normal weight to obese). Metreleptin PK data after subcutaneous (SC) administration in LD patients are available from a small subset of patients in Study FHA101 and from a published study in 7 Japanese patients.

After a single SC dose (0.01 to 0.3 mg/kg) in healthy subjects, metreleptin was rapidly (T_{max} at ~4 hours) and extensively (estimated F=0.94) absorbed, followed by a mono-exponential elimination phase associated with a half-life of approximately 3 to 5 hours. No absolute bioavailability study was conducted; however a high bioavailability was estimated by indirect comparison of PK parameters obtained in different studies after a single 0.3 mg/kg IV and SC dose of metreleptin. Exposure parameters (C_{max} and AUC) increased in proportion to dose after a single IV and SC administration across a dose range (0.01 to 0.3 mg/kg) within the SmPC recommended metreleptin dose range. Peak plasma leptin levels occurred at 2h after dosing in the 7 Japanese patients.

The volume of distribution of metreleptin was reported to be approximately 4 to 5 times plasma volume in healthy adult subjects following IV dosing, which suggests extensive distribution of metreleptin into tissues.

Total body clearance after IV administration was consistent with glomerular filtration rate (GFR) in subjects with normal renal function. The importance of renal elimination is expected taken into account the small size (16 kDa) of metreleptin. Given the elimination profile of metreleptin, the absence of classical *in vitro* studies to investigate hepatic enzyme-mediated metabolism and its interaction potential was considered acceptable.

Nevertheless, leptin is a cytokine and therefore has the potential to alter the formation of cytochrome P450 enzymes. The potential effect of metreleptin on CYP450 enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of metreleptin, in patients being treated with these types of agents, therapeutic monitoring of effect (e.g., warfarin), or drug concentrations (e.g. cyclosporin or theophylline) should be performed and the individual dose of the agent adjusted as needed.

In addition, since it cannot be excluded that metreleptin may reduce exposure to substrates of CYP3A through enzyme induction the efficacy of hormonal contraceptives may be reduced if co-administered with metreleptin. Therefore, an additional non-hormonal contraceptive method should be considered during treatment.

Very limited PK data are available in LD patients. In a comparative analysis between LD patients and healthy subjects (REST120204), the T_{max} was consistent in both populations (~4h), whereas the mean C_{max} and AUC_{0-10h} values for metreleptin were found to be slightly lower in LD patients compared to healthy subjects (approx. 35% for AUC_{0-10h} and 41% for C_{max}). These changes are considered to fall within the variability of the PK of metreleptin.

No accumulation of metreleptin was seen with QD dosing in healthy subjects (study LEPT-970121). However, both in LD patients and healthy subjects, an increase in exposure was observed in the presence of anti-drug antibodies to metreleptin. Noteworthy, the development of ADAs occurred with high incidence in both LD patients and obese subjects. The assumption that high antibody titres increase exposure due to a decrease in renal elimination is considered plausible. The increase in metreleptin exposure with higher antibody titres would be consistent with a decrease in renal elimination of metreleptin in the presence of antibodies to metreleptin.

However, there are still some uncertainties regarding the impact of ADAs on circulating levels of active metreleptin. Different assays were used throughout studies to determine ADAs (RIA, biosensor assay and ECL bridging assay). Samples that were positive for antibodies to metreleptin

for any of the ADA testing methodologies were tested in a cell-based bioassay to evaluate for neutralising activity.

No formal studies have been conducted to evaluate the PK of metreleptin in special populations. Since metreleptin is expected to be primarily renally eliminated and renal diseases are reported to be associated with GL, it is possible that changes in creatinine clearance following metreleptin administration may alter metreleptin exposure. An analysis based on baseline creatinine clearance levels did not reveal any PD effect (change in $HBA1_c$ and triglyceride levels) after 12 months of metreleptin therapy. Based on the above no dose recommendations can be made for patients with renal impairment. Dosing in LD patients will be individually titrated based on metabolic parameters and responses, as well as tolerability; therefore, differences any effect due to differences in renal function can be accounted for through titration of the dose. An additional statement has been included in the SmPC to alert prescribers that pharmacokinetics may be altered in patients with renal impairment.

Based upon the observation that in the general population, females have higher concentrations of leptin compared with males even after adjustment for differences in body composition, the proposed starting dose of metreleptin does differ between males (2.5 mg) and females (5.0 mg) weighing >40 kg

Currently, PK data in children are limited to one patient of 16 years old. However, a safety, efficacy, and PK study to evaluate metreleptin use in paediatric patients <6 years of age is planned as part of the ongoing Paediatric Investigation Plan for metreleptin.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of metreleptin is considered to have been adequately characterised from the submitted data. As there are some uncertainties over the detection of anti-drug antibodies and their potential impact on patients with GL and PL the applicant will investigate this through a detailed immunogenicity strategy. This will involve developing validated assays to better detect this antibodies and collection of samples from a variety of clinical studies.

2.5. Clinical efficacy

2.5.1. Dose response study

Information to support metreleptin dosage instructions has been developed from the long-term efficacy results from Study NIH 991265/20010769. Dosing of metreleptin was empirical and evolved as the investigators gained experience in the NIH trials.

At the time of initiation of the pilot Study 991265, the dose of metreleptin that was proposed to achieve a normal leptin concentration by NIH was 0.03 mg/kg of lean body weight for female children between 14 and 18 years of age, 0.04 mg/kg of lean body weight for adult females, and 0.02 mg/kg of lean body weight for males regardless of age. The doses administered to females were 1.5 to 2 times as high as those given to males based on the known gender dimorphism of leptin levels in healthy subjects, with women having higher leptin levels than men even after adjustment for differences in body.

In the pilot study (NIH 991265), metreleptin treatment was initiated at 50% target dose: total daily dose was 0.02 mg/kg/day in females ≥18 years, and 0.015 mg/kg/day for females <18 years, and 0.01 mg/kg for males regardless of age. The dose was then doubled after 1 month to 100% dose, and then doubled again after an additional 1 month to 200% dose. The daily dose was administered

in 2 equally divided AM and PM doses. The low initial starting dose and conservative titration scheme was used as this was the first such study of metreleptin administration in LD patients; there was uncertainty regarding doses that would be efficacious as well as uncertainty regarding any potential safety or tolerability issues.

The dosing regimen in the long-term Study 20010769 was initially the same as the pilot study. Due to the absence of tolerability issues and the higher dosing to achieve efficacy, dosing of metreleptin evolved to initiating at more efficacious doses with minimal titration. In addition, the protocol was amended to initiate with QD dosing (same total daily dose) instead of BID. In females ≥5 years of age, the modified starting dose was 0.08 to 0.10 mg/kg/day, in females <5 years of age and all males, the starting dose was 0.06 mg/kg/day. Because of the substantial variability in individual metabolic profiles at baseline and differences in response to metreleptin (likely due in large part to sex and LD type), metreleptin doses for each patient were adjusted according to individual response, e.g., increased in an attempt to achieve better efficacy or decreased due to adverse events or effects such as excessive weight loss. All dose escalations were performed in increments of 0.02 mg/kg/day for females 10 years of age and older, and 0.01 mg/kg/day in all other patients.

Based on data from Study NIH 991265/20010769, a fixed initial metreleptin dosing regimen (total daily dose of 5 mg in females and 2.5 mg in males) for patients >40 kg is proposed. The difference in gender in leptin levels is also supported by literature data. A weight-based dosing is proposed for patients with weight <40 kg (total daily dose of mg/kg), which is intended to capture the majority of paediatric patients. 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 listed in **Table 23**.

Table 23. Dosing recommendations for metreleptin therapy for patients with lipodystrophy

SEX/ WEIGHT	STARTING DAILY DOSE (INJECTION VOLUME)	DOSE ADJUSTMENTS (INJECTION VOLUME)	MAXIMUM DAILY DOSE (INJECTION VOLUME)
Males and Females ≤40 kg	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)
Males >40 kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
Females >40 kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)

2.5.2. Main studies

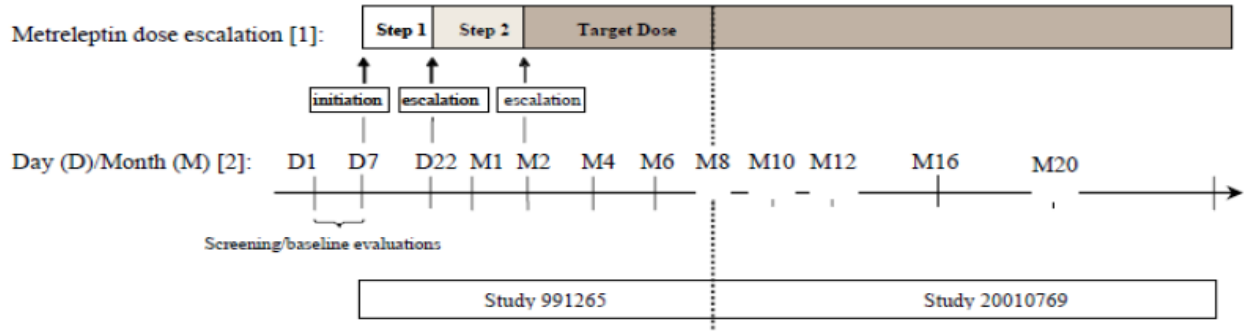
Study NIH 991265/20010769: Long Term Efficacy and Safety of Leptin Replacement in the Treatment of Patients with Lipodystrophy

Methods

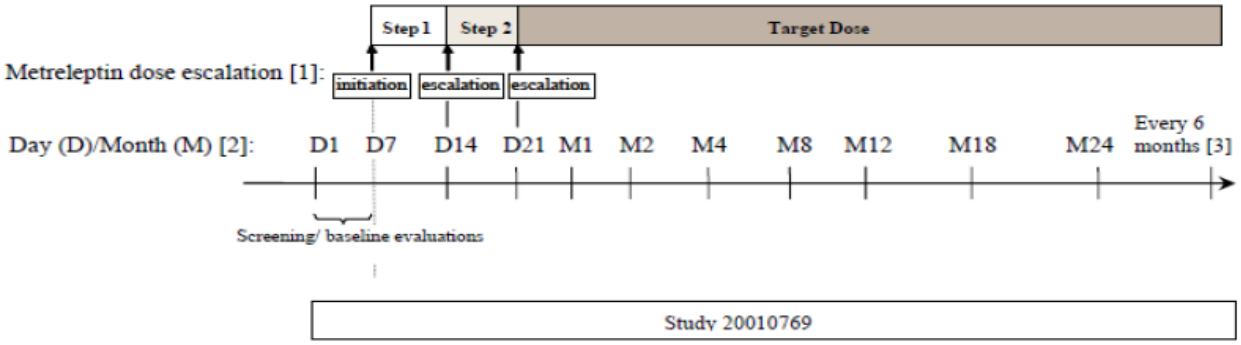
The pilot study (991265) was a dose-escalation study to determine the safety and efficacy of short-term leptin replacement (up to 8 months) and the long-term study (20010769) was conducted to determine the long-term safety and efficacy of metreleptin treatment for patients with LD. Study 20010769 allowed for the rollover of patients from the pilot study, as well as for direct enrolment of new patients. Both studies were open-label.

The design of the study is depicted in **Figure 1**.

Figure 1. Study overview and visit structure for pilot study 991265 (upper panel) and long-term study 20010769



[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.



[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.

Study Participants

Inclusion criteria

1. **Studies 991265/20010769**: males and females of any race/ethnic group

2. Age: **Study 991265**: >5 years of age (modified from >14 years with Amendment 3).

Study 2001769: ≥ 6 months (modified from >5 years with Amendment D).

3. **Studies 991265/20010769**: Clinically significant lipodystrophy identified by the study physician during the physical examination as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient

4. Circulating leptin levels: **Study 991265**: ≤8.0 ng/mL in females and ≤6.0 ng/mL in males (Modified from <4 ng/mL in females and <3 ng/mL in males with Amendment 3)

Study 2001769: <12.0 ng/mL in females and < 8.0 ng/mL in males as measured by Linco assay on a specimen obtained after an overnight fast. In children ages 6 months to 5 years, a circulating leptin level of < 6 ng/mL was used. (Modified from <6 ng/mL in females (original protocol) and < 3 ng/mL (original protocol) or < 4 ng/mL (Amendment B) in males with Amendment C of this protocol, when the leptin levels were modified as noted for patients >5 years of age. Leptin levels for children 6 months to 5 years were added in Amendment D.)

5. **Studies 991265/20010769**: presence of at least 1 of the following metabolic abnormalities:

a) Presence of diabetes as defined by American Diabetes Association criteria (1997 criteria in Study 991265 and Study 2001769 until Amendment D when the 2007 criteria were cited)

i. Fasting plasma glucose ≥ 126 mg/dL (7 mmol/L), or

ii. Two-hour plasma glucose ≥ 200 mg/dL following a 75 g (1.75 g/kg) oral glucose load, or

iii. Diabetic symptoms with a random plasma glucose ≥ 200 mg/dL

b) Studies **991265/20010769**: fasting insulin > 30 µU/mL

c) Fasting hypertriglyceridaemia:

Study 991265: > 200 mg/dL (>2.26 mmol/L)

Study 2001769: > 200 mg/dL (>2.26 mmol/L) or postprandially elevated triglycerides > 500 mg/dL (>5.65 mmol/L) when fasting was clinically not indicated (e.g., in infants). (Modified from >300 mg/dL in the original protocol with Amendment B to >200 mg/dL; postprandial requirement added with Amendment D and inclusion of children 6 months to 5 years).

6. **Study 2001769**: Persons with impaired decision-making capacity and who may have been unable to provide informed consent may have participated in this study per the discretion of the Principal Investigator (added with Amendment I).

Exclusion criteria

- 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;
- Known infectious liver disease (in Study 99165, known liver disease due to causes other than NASH);
- Known human immunodeficiency (HIV) infection (added with Amendment B to Protocol 2001769);
- 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.

Treatments

All recruited patients received metreleptin. Dosing was calculated on a body weight basis and varied by age and sex. As knowledge was gained with metreleptin treatment, the dose and regimen were modified. In the pilot study, the target dose of metreleptin was 0.04 mg/kg/day in females ≥ 18 years, 0.03 mg/kg/day for females < 18 years, and 0.02 mg/kg for males and was to be administered in divided doses twice daily; dosing was 50% of target during Month 1, 100% at Month 2 and 200% at Month 3.

The dosing regimen in Study 20010769 was initially the same as in Study 991265 but was modified to initiate at more typical efficacious doses with minimal titration and dosing frequency changed to once daily. In females ≥ 5 years of age, the modified starting dose was 0.08 to 0.10 mg/kg/day, in females < 5 years of age and all males, the starting dose was 0.06 mg/kg/day. The dose of metreleptin could be increased after the 6-month follow-up. Dose escalations were capped at 0.24 mg/kg/day for any patient without prior approval. If patients did not tolerate a higher dose level, they could continue the study at the next lowest tolerated dose.

Objectives

The objectives of the core protocol for Study 991265 as outlined in the original protocol through the final amendment (Amendment 3) were:

- To determine if metreleptin can be safety administered to a group of patients with clinically significant lipodystrophy;
- To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with clinically significant lipodystrophy.

Additional objectives were to determine if treatment with metreleptin could ameliorate lipid deposition in liver and muscle or improve the hypogonadotropic hypogonadism observed in some patients. Limited data were captured in the study database to assess these objectives.

The main objectives of Study 20010769 as outlined in the final protocol, Expedited Amendment O (with modifications from the original protocol noted) were:

- To determine if metreleptin can be safely administered to patients with lipodystrophy and low leptin levels starting at age 6 months (modified from starting at age 5 years with Amendment D);
- To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with lipodystrophy and leptin deficiency starting at 6 months of age (modified from starting at 5 years of age with Amendment D);
- To determine if metreleptin treatment will be effective in preventing glucose and lipid abnormalities in these young patients;
- To determine if metreleptin treatment will be effective in patients with less severe forms of lipodystrophy (as evidenced by slightly higher circulating leptin concentrations) in terms of improving insulin sensitivity, triglyceride levels and non-alcoholic steatohepatitis (NASH) (as assessed by liver volume, serum markers of liver inflammation and function [added with Amendment D], and liver histopathology);
- To determine if metreleptin treatment will be effective in treating or delaying the development of NASH (as assessed by biochemical markers, liver volume, imaging and liver histopathology [if clinically indicated]);
- To determine effective dose ranges of metreleptin for patients with lipodystrophy (added with Amendment B);
- To devise effective anti-diabetic and lipid-lowering regimens concomitantly with leptin for patients with lipodystrophy and leptin deficiency starting at age 6 months.

Outcomes / endpoints

The co-primary efficacy endpoints in this study were defined as:

- Actual change from baseline in HbA1c at Month 12, and
- Percent change from baseline in fasting serum triglycerides at Month 12

The co-primary efficacy analyses were performed using the Full Analysis Set (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.

Key secondary efficacy endpoints were based on responder analyses at Month 12. These were conducted as a potential indication of clinical benefit to investigate if patients could achieve target reductions in HbA1c or in fasting triglyceride levels by Month 12, as follows.

- 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.

Sample size

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% on-sided alpha error. As noted, the final sample size across the 2 protocols was 107 patients.

Randomisation

Not applicable.

Blinding (masking)

This was an open label study.

Statistical methods

Actual change from baseline in HbA1c and actual and percent change from baseline in fasting triglyceride levels were summarised using descriptive statistics and 95% confidence intervals (CIs). P-values 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. A last observation carried forward (LOCF) method was used to impute any missing Month 12 results. The imputation only included results that were at least 6 months (180 days) post-baseline.

Sensitivity/supportive analyses were performed on the co-primary efficacy endpoints using other pre-specified analysis sets based on exclusion of patients due to major protocol violations or who had modifications in concomitant antidiabetic or lipid lowering therapies that may have had an impact on the efficacy analyses. This included analyses based on all patients in the FAS who had controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (antidiabetic or lipid lowering therapies), through Month 12 and was termed the Controlled Concomitant Medication Full Analysis Set (CFAS). Sensitivity analyses were also performed on the co-primary efficacy endpoints using other analysis sets, including Efficacy Evaluable Analysis Set (EEAS), defined as patients in the FAS who have either efficacy parameter of interest measured at Month 12 and have no major protocol violations prior to Month 12; and Controlled Concomitant Medication EEAS (CEEAS), defined as all patients in the CFAS who have either efficacy parameter of interest measured at Month 12 and have no major protocol violations prior to Month 12.

An additional sensitivity analysis using the FAS on the co-primary endpoints used a worst observation carried forward (WOCF) imputation method.

Key secondary efficacy endpoints were conducted primarily using the FAS with sensitivity analyses performed using the EEAS, CFAS, and CEEAS.

Results

Participant flow

Disposition for the 107 patients enrolled and treated across Studies 991265/20010769 is summarised in **Table 24**.

Table 24. Patient Disposition in Studies 991265/20010769

Disposition Parameter	Generalised Lipodystrophy			Partial Lipodystrophy	
	Males (N=15)	Females (N=51)	Overall (N=66)	PL Subgroup[a] (N=31)	Overall (N=41)
Total Number of Patients:					
Treated	15	51	66	31	41
Premature Discontinuation	7 (46.7)	16 (31.4)	23 (34.8)	11 (35.5)	15 (36.6)
Primary Reason for Premature Discontinuation					
Noncompliance	2 (13.3)	3 (5.9)	5 (7.6)	6 (19.4)	6 (14.6)
Death	0	3 (5.9)	3 (4.5)	1 (3.2)	1 (2.4)
Ineligibility Determined	2 (13.3)	0	2 (3.0)	0	0
Adverse Event	0	1 (2.0)	1 (1.5)	0	0
Lost to Follow-up	0	1 (2.0)	1 (1.5)	0	0
Other:	3 (20.0)	8 (15.7)	11 (16.7)	4 (12.9)	8 (19.5)
Transferred to Other Program	3	5	8	1	2
Lack of Efficacy/ No Benefit	0	1	1	3	5
Other[b]	0	2	2	0	1
Patients contacted for follow-up[c]	**6 (40.0)**	**32 (62.7)**	**38 (57.6)**	**20 (64.5)**	**26 (63.4)**

Abbreviations: 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 United States were contacted to determine if and how they were able to continue on therapy.

Recruitment

Study start date: 24 July 2000 (First patient enrolled)

Study completion date: 26 March 2014 (Last patient enrolled)

Conduct of the study

As this was an investigator-sponsored clinical trial, there was no systematic collection of protocol deviation data. Significant protocol violations that became apparent upon review of the data and that led to exclusion of patient data from the efficacy evaluable analysis sets primarily related to prolonged dose interruptions, baseline leptin levels above the required eligibility criteria, and on-study pregnancies with continued treatment.

A total of 26 patients were noted to have a major protocol violation, including 16 patients (24%) with GL and 10 patients (24%) with PL, including 8 (26%) in the PL subgroup. The most common violations were dose interruptions >2 weeks, reported during the first 12 months of treatment in 6 GL patients and after Month 12 in 7 patients with GL and 5 patients with PL.

There were 3 amendments for Study 991265. The key changes implemented by protocol amendment were to increase the duration of the study from 4 to 8 months, extended treatment duration beyond 8 months or until the patient enrolled into Study 20010769 and minimum age for inclusion (from >14 years to >5 years) and for patients with higher leptin levels (from <3 ng/mL to ≤6 ng/mL in males and from <4 ng/mL to ≤ 8 in females). However, all patients enrolled under this protocol were >14 years of age and had leptin levels <4 ng/mL at baseline.

Over the course of 14 years, a total of 15 amendments were made to the original protocol for Study 2001769. The key changes implemented by protocol amendment are concerning increase of the sample size, starting dose (no longer required dose escalation), dosing regimen BID-QD, baseline leptin levels upper limit (6 ng/mL to 12 ng/mL for females and from 4 ng/mL to 8 ng/mL for males), minimum age for inclusion (from >5 years to >6 months), exclusion of PL patients with haematologic abnormalities. Note that as required by the NIH review committee, the protocols underwent annual reviews and at each review were listed as protocol amendment regardless of where changes were or were not implemented.

Baseline data

Patient demographic and baseline characteristics, medication use and metabolic characteristics are summarised for the Safety Analysis Set in **Table 25, Table 26** and **Table 27**. The data are very similar for the Full Analysis Set (not shown) since these populations differed by only 5 patients.

Table 25. Patient demographic and baseline characteristics summarised for the SAS in in Studies 991265/20010769

Demographic and Baseline Characteristic:	Generalised Lipodystrophy			Partial Lipodystrophy	
	Males (N=15)	Females (N=51)	Overall (N=66)	PL Subgroup[a] (N=31)	Overall (N=41)
Sex, n (%)					
Male	15 (100.0)	0	15 (22.7)	1 (3.2)	1 (2.4)
Female	0	51 (100.0)	51 (77.3)	30 (96.8)	40 (97.6)
Race, n (%)					
Caucasian	7 (46.7)	24 (47.1)	31 (47.0)	26 (83.9)	36 (87.8)
Black	2 (13.3)	14 (27.5)	16 (24.2)	0	0
Asian	1 (6.7)	2 (3.9)	3 (4.5)	1 (3.2)	1 (2.4)
Native American	0	2 (3.9)	2 (3.0)	0	0
Hispanic	5 (33.3)	6 (11.8)	11 (16.7)	2 (6.5)	2 (4.9)
Other	0	3 (5.9)	3 (4.5)	2 (6.5)	2 (4.9)
Age (years), n	15	51	66	31	41
Mean (SD)	19.5 (18.10)	17.3 (10.63)	17.8 (12.59)	37.0 (14.37)	34.1 (14.64)
Median	13.0	16.0	15.0	38.0	34.0
Range	1.0, 68.0	2.0, 59.0	1.0, 68.0	15.0, 64.0	10.0, 64.0
Age Group (years), n (%)					
<2	1 (6.7)	0	1 (1.5)	0	0
≥2 to <6	0	4 (7.8)	4 (6.1)	0	0
≥6 to <12	5 (33.3)	7 (13.7)	12 (18.2)	0	2 (4.9)
≥12 to <18	5 (33.3)	23 (45.1)	28 (42.4)	5 (16.1)	6 (14.6)
<18	11 (73.3)	34 (66.7)	45 (68.2)	5 (16.1)	8 (19.5)
≥18	4 (26.7)	17 (33.3)	21 (31.8)	26 (83.9)	33 (80.5)
Lipodystrophy Type, n (%)					
Acquired	7 (46.7)	14 (27.5)	21 (31.8)	4 (12.9)	6 (14.6)
Congenital/Familial	8 (53.3)	37 (72.5)	45 (68.2)	27 (87.1)	35 (85.4)
Fasting Leptin (ng/mL), n	15	49	64	31	41
Mean (SD)	1.0 (0.74)	1.4 (1.03)	1.3 (0.98)	6.7 (3.70)	6.4 (3.52)
Median	1.0	1.1	1.0	5.9	5.9
Range	0.3, 3.3	0.2, 5.3	0.2, 5.3	1.6, 16.9	1.0, 16.9
Weight Category (kg), n					
≤40 kg	4 (26.7)	14 (27.5)	18 (27.3)	0	1 (2.4)
>40 kg	11 (73.3)	37 (72.5)	48 (72.7)	31 (100.0)	40 (97.6)
BMI (kg/m^2), n	15	49	64	31	41
Mean (SD)	20.9 (3.90)	20.6 (3.45)	20.7 (3.53)	25.5 (3.82)	25.8 (4.09)
Median	20.0	20.6	20.5	25.1	25.3
Range	14.0, 26.9	14.1, 29.5	14.0, 29.5	18.6, 33.3	17.7, 33.3

Abbreviations: BMI = body mass index; HbA1c = haemoglobin A1c; PL = partial lipodystrophy; SD = standard deviation

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

Table 26. Baseline medication use in Studies 991265/20010769

Baseline Medication	Generalised Lipodystrophy			Partial Lipodystrophy	
	Males (N=15) n (%)	Females (N=51) n (%)	Overall (N=66) n (%)	PL Subgroup[a] (N=31) n (%)	Overall (N=41) n (%)
Anti-diabetic Medication[b]	**11 (73.3)**	**42 (82.4)**	**53 (80.3)**	**30 (96.8)**	**37 (90.2)**
Any Insulin	6 (40.0)	33 (64.7)	39 (59.1)	17 (54.8)	20 (48.8)
Insulin Alone	4 (26.7)	15 (29.4)	19 (28.8)	6 (19.4)	6 (14.6)
Insulin plus Oral Agent	2 (13.3)	18 (35.3)	20 (30.3)	10 (32.3)	13 (31.7)
Oral Agent Only	5 (33.3)	7 (13.7)	12 (18.2)	12 (38.7)	15 (36.6)
Oral Anti-diabetic Medications	7 (46.7)	25 (49.0)	32 (48.5)	22 (71.0)	28 (68.3)
Biguanides	7 (46.7)	24 (47.1)	31 (47.0)	17 (54.8)	23 (56.1)
Thiazolidinediones	0	2 (3.9)	2 (3.0)	12 (38.7)	15 (36.6)
Sulfonylureas	0	0	0	5 (16.1)	6 (14.6)
Lipid Lowering Therapies[b]	6 (40.0)	28 (54.9)	34 (51.5)	26 (83.9)	34 (82.9)
HMG CoA Reductase Inhibitors	3 (20.0)	8 (15.7)	11 (16.7)	12 (38.7)	13 (31.7)
Other Lipid Modifying Agents	1 (6.7)	9 (17.6)	10 (15.2)	15 (48.4)	19 (46.3)
Fibrates	3 (20.0)	22 (43.1)	25 (37.9)	17 (54.8)	21 (51.2)
Other Concomitant Medications[c]					
Lisinopril	2 (13.3)	7 (13.7)	9 (13.6)	7 (22.6)	9 (22.0)
Acetylsalicylic acid	1 (6.7)	4 (7.8)	5 (7.6)	7 (22.6)	7 (17.1)
Enalapril	2 (13.3)	5 (9.8)	7 (10.6)	3 (9.7)	4 (9.8)
Multivitamins	0	4 (7.8)	4 (6.1)	5 (16.1)	6 (14.6)
Cholecalciferol	1 (6.7)	1 (2.0)	2 (3.0)	5 (16.1)	5 (12.2)
Ergocalciferol	0	1 (2.0)	1 (1.5)	3 (9.7)	6 (14.6)

Abbreviations: ATC = anatomic therapeutic class; HbA1c = haemoglobin A1c; PL = partial lipodystrophy; WHODD = World Health Organisation Drug Dictionary

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

b Terms across multiple WHODD ATC classes are grouped to provide overall incidence

c Individual WHODD preferred terms reported with incidence >10% in GL or PL groups.

Source: Table 14.1.3.1A, Table 14.3.6.2, and Table 14.3.6.5

Table 27. Baseline metabolic characteristics in Studies 991265/20010769

Baseline Laboratory Values:	Generalised Lipodystrophy			Partial Lipodystrophy	
	Males (N=15)	Females (N=51)	Overall (N=66)	PL Subgroup[a] (N=31)	Overall (N=41)
HbA1c (%), n	15	49	64	31	41
Mean (SD)	8.1 (2.52)	8.8 (2.25)	8.6 (2.32)	8.8 (1.88)	8.0 (2.15)
Median	8.4	8.7	8.7	8.6	7.8
Min, Max	4.5, 13.0	4.5, 13.7	4.5, 13.7	5.7, 13.3	4.6, 13.3
HbA1c (%), n (%)					
<6.5	6 (40.0)	9 (17.6)	15 (22.7)	2 (6.5)	12 (29.3)
≥6.5	9 (60.0)	40 (78.4)	49 (74.2)	29 (93.5)	29 (70.7)
≥7.0	9 (60.0)	40 (78.4)	49 (74.2)	26 (83.9)	26 (63.4)
≥8.0	9 (60.0)	33 (64.7)	42 (63.6)	19 (61.3)	19 (46.3)
Fasting TG (mmol/L), n	15	48	63	31	41
Mean (SD)	4.8 (6.18)	17.6 (28.16)	14.5 (25.29)	14.8 (25.72)	12.0 (22.85)
Median	2.5	5.5	4.6	5.5	4.1
Min, Max	1.1, 25.3	0.6, 143.3	0.6, 143.3	1.2, 109.5	1.1, 109.5
Fasting TG, n (%)					
<2.26 mmol/L	6 (40.0)	7 (13.7)	13 (19.7)	4 (12.9)	7 (17.1)
≥2.26 mmol/L	9 (60.0)	41 (80.4)	50 (75.8)	27 (87.1)	34 (82.9)
≥2.26 to <5.65 mmol/L	6 (40.0)	18 (35.5)	24 (36.4)	12 (38.7)	19 (46.3)
≥5.65 mmol/L	3 (20.0)	23 (45.1)	26 (39.4)	15 (48.4)	15 (36.6)
Composite HbA1c and/or TG, n (%)					
HbA1c <6.5% and					
TG <2.26 mmol/L	4 (26.7)	2 (3.9)	6 (9.1)	0	3 (7.3)
TG ≥2.26 mmol/L	2 (13.3)	7 (13.7)	9 (13.6)	2 (6.5)	9 (22.0)
TG <5.65 mmol/L	5 (33.3)	8 (15.7)	13 (19.7)	0	10 (24.4)
TG ≥5.65 mmol/L	1 (6.7)	1 (2.0)	2 (3.0)	2 (6.5)	2 (4.9)
HbA1c ≥6.5% and					
TG <2.26 mmol/L	2 (13.3)	5 (9.8)	7 (10.6)	4 (12.9)	4 (9.8)
TG ≥2.26 mmol/L	7 (46.7)	34 (66.7)	41 (62.1)	25 (80.6)	25 (61.0)
TG <5.65 mmol/L	7 (46.7)	17 (33.3)	24 (36.4)	16 (51.6)	16 (39.0)
TG ≥5.65 mmol/L	2 (13.3)	22 (43.1)	24 (36.4)	13 (41.9)	13 (31.7)
HbA1c ≥6.5% and/or					
TG ≥2.26 mmol/L	11 (73.3)	47 (92.2)	58 (87.9)	31 (100.0)	38 (92.7)
TG ≥5.65 mmol/L	10 (66.7)	41 (80.4)	51 (77.3)	31 (100.0)	31 (75.6)

Fasting Glucose (mmol/L), n	15	49	64	31	41
Mean (SD)	9.0 (4.46)	10.7 (5.19)	10.3 (5.04)	9.9 (4.33)	8.7 (4.35)
Median	7.0	9.7	8.7	8.8	7.0
Min, Max	3.9, 18.4	3.6, 26.5	3.6, 26.5	5.0, 20.4	2.7, 20.4
Fasting Glucose, n (%)					
< 5.55 mmol/L	3 (20.0)	8 (15.7)	11 (16.7)	5 (16.1)	11 (26.8)
≥5.55 to <6.99 mmol/L	4 (26.7)	6 (11.8)	10 (15.2)	4 (12.9)	8 (19.5)
≥6.99 mmol/L	8 (53.3)	35 (68.6)	43 (65.2)	22 (71.0)	22 (53.7)
ALT, n (%)					
≤ULN	2 (13.3)	13 (25.5)	15 (22.7)	22 (71.0)	27 (65.9)
>ULN	13 (86.7)	36 (70.6)	49 (74.2)	9 (29.0)	14 (34.1)
AST, n (%)					
≤ULN	5 (33.3)	23 (45.1)	28 (42.4)	24 (77.4)	31 (75.6)
>ULN	10 (66.7)	26 (51.0)	36 (54.5)	7 (22.6)	10 (24.4)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HbA1c = hemoglobin A1c fraction; PL = partial lipodystrophy; SD = standard deviation; TG = triglycerides; ULN = upper limit of normal

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

Numbers analysed

An overview of the analysis datasets used for evaluation of safety and efficacy endpoints is provided in **Table 28.**

Table 28. Datasets analysed in in Studies 991265/20010769

	GENERALISED LIPODYSTROPHY			PARTIAL LIPODYSTROPHY	
ANALYSIS SETS	MALES (N=15)	FEMALES (N=51)	OVERALL (N=66)	PL SUBGROUP[a] (N=31)	OVERALL (N=41)
Safety Analysis Set[b]	15 (100.0)	51 (100.0)	66 (100.0)	31 (100.0)	41 (100.0)
Full Analysis Set[c]	15 (100.0)	47 (92.2)	62 (93.9)	30 (96.8)	40 (97.6)
Controlled Concomitant Medication Full Analysis Set[d]	14 (93.3)	40 (78.4)	54 (81.8)	23 (74.2)	31 (75.6)
Efficacy-Evaluable Analysis Set[e]	8 (53.3)	30 (58.8)	38 (57.6)	19 (61.3)	28 (68.3)
Controlled Concomitant Medication Efficacy-Evaluable Analysis Set[f]	8 (53.3)	25 (49.0)	33 (50.0)	13 (41.9)	20 (48.8)
Antibody Analysis Set[g]	5 (33.3)	33 (64.7)	38 (57.6)	8 (25.8)	12 (29.3)

Abbreviations: CM = concomitant medication; HbA1c = haemoglobin A1c; PL = partial lipodystrophy

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

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 Full Analysis Set who have either efficacy parameter of interest measured at Month 12 and do not have major protocol violations prior to Month 12.

f 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.

g All patients in the Safety Analysis Set who have antibody status assessed at least once on study.

Outcomes and estimation

Co-primary endpoints: HbA1c and Triglycerides

Results for the analysis of the primary efficacy endpoints of actual changes from baseline to Month 12 in HbA1c and actual and percent changes for baseline in triglycerides using LOCF (after Month 6/Day 180) for the FAS are presented in **Table 29**.

Table 29. Primary Efficacy Endpoints: Change from Baseline to Month 12 in HbA1c and Fasting Triglycerides using LOCF (FAS Population, Studies 991265/20010769)

Parameter Statistic	Generalised Lipodystrophy			Partial Lipodystrophy	
	Males (N=15)	Females (N=47)	Overall (N=62)	PL Subgroup[a] (N=30)	Overall (N=40)
HbA1C (%)					
BL Value, n	15	47	62	30	40
Mean (SD)	8.1 (2.52)	8.7 (2.27)	8.6 (2.33)	8.7 (1.90)	7.9 (2.16)
Median	8.4	8.7	8.7	8.6	7.7
Min, Max	4.5, 13.0	4.5, 13.7	4.5, 13.7	5.7, 13.3	4.6, 13.3
Month 12 Value, n	14	45	59	28	37
Mean (SD)	6.2 (1.41)	6.5 (1.76)	6.4 (1.68)	7.9 (1.81)	7.4 (1.82)
Median	5.7	6.1	6.0	7.4	7.1
Min, Max	4.7, 9.0	4.4, 12.8	4.4, 12.8	6.0, 12.7	4.8, 12.7
Actual Change from BL, n	14	45	59	28	37
Mean (SD)	-1.9 (2.34)	-2.2 (2.10)	-2.2 (2.15)	-0.9 (1.22)	-0.6 (1.21)
[95% CI]	[-3.2, -0.5]	[-2.9, -1.6]	[-2.7, -1.6]	[-1.4, -0.4]	[-1.0, -0.2]
p-value[b]	0.011	<0.001	<0.001	<0.001	0.005
Fasting TG (mmol/L)					
BL Value, n	15	46	61	30	40
Mean (SD)	4.8 (6.18)	17.9 (28.70)	14.7 (25.66)	15.2 (26.07)	12.2 (23.10)
Median	2.5	5.5	4.6	5.6	4.3
Min, Max	1.1, 25.3	0.6, 143.3	0.6, 143.3	1.2, 109.5	1.1, 109.5
Month 12 Value	14	44	58	28	37
Mean (SD)	1.8 (0.95)	5.3 (6.78)	4.5 (6.10)	7.2 (10.19)	6.3 (8.99)
Median	1.7	2.8	2.3	3.6	3.6
Min, Max	0.6, 3.5	0.7, 31.9	0.6, 31.9	1.0, 41.2	1.0, 41.2
% Change from BL, n	14	43	57	28	37
Mean (SD)	-29.8 (41.70)	-32.9 (78.96)	-32.1 (71.28)	5.7 (229.95)	11.3 (201.21)
[95% CI]	[-53.9, -5.7]	[-57.2, -8.6]	[-51.0, -13.2]	[-83.5, 94.9]	[-55.8, 78.4]
p-value[b]	0.019	0.009	0.001	0.897	0.734

Abbreviations: BL = baseline; CI = confidence interval; FAS = Full Analysis Set; HbA1c = haemoglobin A1c; LOCF = last observation carried forward; max = maximum; min = minimum; PL = partial lipodystrophy; SD = standard deviation; TG = triglycerides

Note: LOCF imputation method only includes results that are at least 6 months (180 days) post baseline.

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

b P-values computed using paired t-tests.

Following review of individual patient data for outlier results, it was noted that 1 patient, had a >1000% increase from baseline to Month 12 for triglyceride levels; the only patient in the study with this level of change at Month 12. This patient entered the trial with a triglyceride level of 3.0 mmol/L, which increased to 18.6 mmol/L at month 6 and to 37.7 mmol/L at month 12.

This patient was terminated from the study by the Investigator 2 days prior to the Month 12 assessment for noncompliance with study drug administration. Based on this, an ad hoc analysis was conducted for the FAS excluding this patient's data **Table 30**.

Table 30. Primary efficacy endpoints: Change from baseline to month 12 in HbA1c and fasting triglycerides using LOCF for the PL subgroup and overall PL Group (FAS Population, Excluding patient 901-080, Studies 991265/20010769)

PARAMETER STATISTIC	PARTIAL LIPODYSTROPHY	
	PL SUBGROUP[a] (N=29)[b]	OVERALL (N=39)[b]
HbA1C (%)		
BL Value, n	29	39
Mean (SD)	8.8 (1.91)	8.0 (2.18)
Median	8.6	7.8
Min, Max	5.7, 13.3	4.6, 13.3
Month 12 Value, n	27	36
Mean (SD)	8.0 (1.83)	7.5 (1.84)
Median	7.5	7.2
Min, Max	6.0, 12.7	4.8, 12.7
Actual Change from BL, n	27	36
Mean (SD)	-0.9 (1.23)	-0.6 (1.22)
[95% CI]	[-1.4, -0.4]	[-1.0, -0.2]
p-value[c]	<0.001	0.005
Fasting TG (mmol/L)		
BL Value, n	29	39
Mean (SD)	15.7 (26.42)	12.5 (23.35)
Median	5.7	4.6
Min, Max	1.2, 109.5	1.1, 109.5
Month 12 Value	27	36
Mean (SD)	6.0 (8.41)	5.4 (7.37)
Median	3.4	3.5
Min, Max	1.0, 41.2	1.0, 41.2

% Change from BL, n	27	36
Mean (SD)	-37.4 (30.81)	-20.8 (47.93)
[95% CI]	[-49.6, -25.2]	[-37.1, -4.6]
p-value[c]	<0.001	0.013

Abbreviations: BL = baseline; CI = confidence interval; FAS = Full Analysis Set; HbA1c = haemoglobin A1c; LOCF = last observation carried forward; max = maximum; min = minimum; PL = partial lipodystrophy; SD = standard deviation; TG = triglycerides

Note: LOCF imputation method only includes results that are at least 6 months (180 days) post baseline.

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 (Listing 16.2.6.1A). The patient was terminated from treatment by the Investigator for noncompliance with dosing (Listing 16.2.1.1).

c P-values computed using paired t-tests.

Key secondary endpoint: Fasting Glucose Levels

In general, changes in fasting plasma glucose followed a similar pattern as changes in HbA1c. Among the patients with GL included in the FAS, treatment with metreleptin led to clinically meaningful and statistically significant reductions in fasting glucose; mean glucose levels were reduced from 10.2 mmol/L at baseline to 7.0 mmol/L at Month 12/LOCF, a mean change of -3.0 mmol/L ($p<0.001$), representing a 20% decrease in fasting glucose levels. Females had a greater reduction in fasting glucose levels (-3.4 mmol/L), which was statistically significant ($p<0.001$) compared to males (-1.6 mmol/L; $p=0.191$). This may be related to a lower baseline glucose level in males compared to females (9.0 vs 10.5 mmol/L); note that mean fasting glucose levels at Month 12/LOCF were comparable in males and females (7.1 and 7.0 mmol/L, respectively).

Results in the PL subgroup were similar to the GL group for the FAS; in the PL subgroup, mean baseline glucose levels were 10.0 mmol/L with a reduction to a mean level of 8.1 mmol/L at Month 12/LOCF, a mean change of -1.8 mmol/L ($p = 0.003$), representing a 13% decrease from baseline. Mean changes in the overall PL group were also statistically significant but of lower magnitude (-1.2 mmol/L; $p = 0.012$).

Key secondary efficacy endpoint: target reductions in HbA1c or triglycerides

Nearly 80% of patients in the FAS with GL had 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. The percent of females with GL who achieved these target levels was higher than that of males, although 71% of male GL patients had a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12 with 50% achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides at Month 12/LOCF.

Results were consistent in the PL subgroup for the FAS, with 68% of patients in the PL subgroup 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. In the CFAS for the PL subgroup, 55% had a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 27% achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides at that time.

Secondary / exploratory endpoints

Mean changes in other lipid parameters, including total cholesterol and LDL-C, were consistent with those reported for triglycerides with mean reductions noted to Month 12/LOCF for both parameters; little to no change was noted for HDL-C.

In the GL group, mean changes to Month 12/LOCF of -2.3 and -0.9 mmol/L were noted for total cholesterol and LDL-C, respectively, representing mean percent changes of -28% and -24%. Reductions in total cholesterol were greater for female patients with GL compared with males, whereas reductions in LDL-C were similar. 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).

Most patients in the GL group entered the study with elevated hepatic transaminase levels (74% with ALT >ULN and 55% with AST >ULN). In these patients, substantial reductions in both ALT and AST occurred during treatment with metreleptin. Mean change in the GL group from baseline to Month 12/LOCF in ALT was -53.1 U/L; the changes were observed early with a mean change to Month 4 in GL patients of -42.1 U/L. Similar results were observed for AST with a mean change in the GL group to Month 4 of -23.3 U/L and to Month 12/LOCF of -23.8 U/L. The reductions were more notable in male patients with GL, as a higher percent of male patients entered the study with elevated transaminase levels (87% and 67% with ALT and AST >ULN, 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). 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.

Among the 21 patients with GL who could be assessed for changes from baseline in liver volume, 15 (71%) had reductions observed at all post-baseline assessments (4 of these patients had only 1 or 2 assessments post baseline) and an additional 4 patients had reductions at all assessments on or after Month 12 of treatment. Reductions in liver volume for these 19 patients ranged from 7% to 71%, with most patients (12 of 19) having reductions in liver volume ≥30%. The remaining 2 patients with GL who had baseline and post-baseline results did show reductions in liver volume but not at all assessments.

Among the 8 patients in the PL subgroup, 4 (50%) had reductions observed at all post-baseline assessments (1 of these patients had only 2 assessments post-baseline) 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%. The remaining 3 patients in the PL subgroup who had baseline and post-baseline results did show reductions in liver volume but not at all assessments.

13 of the 30 patients with data available for analysis of changes in liver volume were <18 years of age. Reductions from baseline were observed at all assessments in 10 (77%) of these 13 paediatric patients (2 had only 1 or 2 post-baseline assessments); the remaining 3 patients had reductions at all assessments after Month 12. Reductions ranged from 7% to 64% with most patients (8 of 13) having reductions ≥30%. Consistent with these results, the mean (SD) reduction from baseline to Month 12 in liver volume for the 7 patients <18 years of age who could be assessed (all were patients with GL) was -35.1%.

Oral glucose tolerance tests (1.75 g/kg glucose up to 75 g ingested orally) were performed to assess the effect of metreleptin on glucose tolerance. After 4 months of metreleptin therapy, both fasting (time 0) and 3-hour glucose levels were reduced with further reductions at Month 8. These results were sustained through 12 months of therapy. Consistent with these results, the mean (SD) average changes in glucose levels across all time points (0 to 180 minutes) during the OGTT from baseline to Months 4, 8, and 12 for GL patients were -2.2 (5.28) mmol/L, -3.5 (4.46) mmol/L, and -4.2 (5.23) mmol/L, respectively. Data were available for 20 and 24 patients at months 4 and 8 respectively, compared to 49 available at baseline and month 12.

For the PL subgroup, data were only available for 9 and 12 patients at Months 4 and 8, respectively, compared to 28 and 20 patients with data available at baseline and Month 12. The mean (SD) average changes in glucose levels across all time points (0 to 180 minutes) during the OGTT from

baseline to Months 4, 8 and 12 for patients in the PL subgroup were -2.5 (1.34) mmol/L, -0.4 (3.70) mmol/L, and -0.8 (2.40) mmol/L, respectively. Results were more variable in this subgroup of patients, although the curve for Month 12 is consistently below that of the baseline curve.

Plasma glucose profiles in response to an insulin tolerance test (injection of 0.2 U insulin/kg body weight) for the GL group show that mean glucose profile in response to an intravenous insulin challenge was substantially lower after Month 4 of metreleptin treatment, consistent with increased insulin sensitivity, with similar results observed at Months 8 and Month 12 of treatment in the GL group. Results were similar in the PL subgroup, although the data were more limited.

The effect of metreleptin on fasting insulin concentrations (a marker of insulin resistance) was examined in those patients who were not receiving concomitant insulin therapy. Median changes from baseline to Month 12/LOCF in fasting insulin concentrations were -20.6 mU/L among the 28 patients in the GL group with data included in the analysis and 1.5 mU/L among the 14 patients in the PL subgroup with data available.

Ancillary analyses

The potential effect of baseline levels of HbA1c and triglycerides on response to metreleptin was evaluated; both changes from baseline in these 2 parameters and responder analyses were produced. Results for these analyses for the overall GL group are provided in **Table 31** and **Table 32**.

Table 31. Change from baseline to month 12/LOCF in HbA1c and fasting triglycerides using LOCF by baseline metabolic abnormalities (FAS Population, excluding patient 901-080, Studies 991265/20010769)

	GENERALISED LIPODYSTROPHY GROUP				PARTIAL LIPODYSTROPHY SUBGROUP[a,b]			
	HbA1c		Triglycerides		HbA1c		Triglycerides	
BASELINE LEVELS:	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
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)
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)
HbA1c (%) and/or Triglycerides (mmol/L)								
≥6.5% and/or ≥2.26 mmol/L	53	-2.4 (2.14)	51	-39.1 (71.28)	27	-0.9 (1.23)	27	-37.4 (30.81)
≥6.5% and/or ≥5.65 mmol/L	47	-2.7 (2.10)	45	-42.9 (72.71)	27	-0.9 (1.23)	27	-37.4 (30.81)

Abbreviations: Δ = change; FAS = Full Analysis Set; HbA1c = haemoglobin A1c; 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 (Listing 16.2.6.1A). The patient was terminated from treatment by the Investigator for noncompliance with dosing (Listing 16.2.1.1).

Table 32. Responder Analysis: Patients who met target reductions in HbA1c or triglycerides at month 12/LOCF by baseline metabolic abnormality (FAS Population, Studies 991265/20010769)

	Generalised Lipodystrophy Target Reduction to Month 12 of:			Partial Lipodystrophy[a] Target Reduction to Month 12 of:		
	≥1% HbA1c or ≥30% TG	≥1.5% HbA1c or ≥35% TG	≥2% HbA1c or ≥40% TG	≥1% HbA1c or ≥30% TG	≥1.5% HbA1c or ≥35% TG	≥2% HbA1c or ≥40% TG
Subgroup	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)	n/N1 (%)
HbA1c						
<6.5%	5/14 (35.7)	4/14 (28.6)	4/14 (28.6)	1/2 (50.0)	1/2 (50.0)	1/2 (50.0)
≥6.5%	42/45 (93.3)	40/45 (88.9)	35/45 (77.8)	18/26 (69.2)	13/26 (50.0)	11/26 (42.3)
≥7%	42/45 (93.3)	40/45 (88.9)	35/45 (77.8)	16/23 (69.6)	12/23 (52.2)	11/23 (47.8)
≥8%	37/39 (94.9)	35/39 (89.7)	30/39 (76.9)	15/18 (83.3)	12/18 (66.7)	11/18 (61.1)
Triglycerides						
<2.26 mmol/L	7/13 (53.8)	6/13 (46.2)	5/13 (38.5)	2/3 (66.7)	1/3 (33.3)	1/3 (33.3)
≥2.26 mmol/L	39/45 (86.7)	37/45 (82.2)	34/45 (75.6)	17/25 (68.0)	13/25 (52.0)	11/25 (44.0)
≥5.65 mmol/L	23/24 (95.8)	23/24 (95.8)	22/24 (91.7)	13/15 (86.7)	11/15 (73.3)	10/15 (66.7)
HbA1c (%) and/or Triglycerides (mmol/L)						
≥6.5% and/or ≥2.26 mmol/L	47/53 (88.7)	44/53 (83.0)	39/53 (73.6)	19/28 (67.9)	14/28 (50.0)	12/28 (42.9)
≥6.5% and/or ≥5.65 mmol/L	44/47 (93.6)	42/47 (89.4)	37/47 (78.7)	19/28 (67.9)	14/28 (50.0)	12/28 (42.9)

Abbreviations: FAS = Full Analysis Set; HbA1c = haemoglobin A1c; LOCF = last observation carried forward; n = number of responders; N1 = number in FAS evaluated at Month 12/LOCF; PL = partial lipodystrophy; TG = triglycerides

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

Post-hoc tabulations were also produced for patients with PL from NIH 991265/20010769 based on leptin cut points of <4 ng/mL and ≥4 to <12 ng/mL that include patients with baseline HbA1c ≥6.5% (initially proposed PL subgroup by the applicant) and >8% (Multi-Society Practice Guidelines (MSPG) cut-off point) and/or who had baseline triglycerides ≥5.65 mmol/L.

Changes from baseline to Month 12/LOCF for HbA1c and triglycerides were examined for

- the Sponsor-defined PL subgroup (HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L): patients with baseline leptin <4 ng/mL and ≥4 to <12 ng/mL
- the subset of PL patients who met the MSPG criteria (leptin <4 ng/mL, HbA1c >8.0% and/or triglycerides ≥5.65mmol/L) patients with baseline leptin <4 ng/mL and ≥4 to <12 ng/mL

Table 33. Post-hoc analysis of percent change in HbA1c and TG, according to leptin levels, HbA1c and TG at baseline (FAS Population, Studies 991265/20010769)

Subset	HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L		HbA1c >8.0% and/or triglycerides ≥5.65mmol/L	
	Leptin < 4ng/mL (n=8)	Leptin ≥ 4 to < 12 ng/mL (n=17)	Leptin < 4ng/mL (n=7)	Leptin ≥ 4 to < 12 ng/mL (n=12)
Mean % change BL to month 12/LOCF in HbA1c	-0.9%	-1.0%	-0.9%	-1.2%
Mean % change BL to month 12/LOCF in TG	-37.8%	-43.1%	-38.9%	-54.3%

Results of the analyses of changes in HbA1c from baseline to Month 12/LOCF for all PL patients included in the FAS from the NIH 991265/20010769 study with baseline leptin values of ≤4 ng/mL, >4 ng/mL and ≤10 ng/mL, >10 ng/mL and <12 ng/mL, ≥12 ng/mL were also presented in **Table 34**.

Table 34. Mean change from BL in HbA1C to month 12/LOCF for all PL patients from FAS population in NIH 991265/20010769 (SD)

	<6.5	≥6.5 AND <7	≥7 AND <8	≥8
Leptin ≤4 ng/mL	0.2 (0.39) (n=4)	NA	-0.9 (NA) (n=1)	-1.4 (0.80) (n=5)
Leptin >4 and ≤10 ng/mL	0.4 (0.54) (n=8)	-0.4 (0.21) (n=2)	-0.2 (0.95) (n=3)	-1.3 (1.76) (n=9)
Leptin >10 and <12 ng/mL	NA	NA	0.0 (NA) (n=1)	-1.8 (1.20) (n=2)
Leptin ≥12 ng/mL	NA	-0.1 (NA) (n=1)	NA	-0.7 (0.28) (n=2)

Results by Binding Antibody Response

An overview of ADA status by study for patients with lipodystrophy in studies NIH 991265/20010769 and FHA101 was provided in **Table 35**.

Table 35. Overview of Anti-Drug Antibody status by study and overall for patients with lipodystrophy

PATIENT STATUS	NIH991265/200107 69 STUDIES	FHA101 STUDY	TOTAL
Patients Enrolled	107	41	148
GL and PL Patients with Antibody Data	81	21	102
Anti-metreleptin Antibody Negative	4	0	4
Anti-metreleptin Antibody Positive	77	21	98
Sustaining Non-Neutralising Antibodies	43	17	60
Neutralising	34	4	38
GL Patients with Antibody Data	50	3	53
Anti-metreleptin Antibody Negative	2	0	2
Anti-metreleptin Antibody Positive	48	3	51
Neutralising	25	0	25
PL Patients with Antibody Data	31	18	49
Anti-metreleptin Antibody Negative	2	0	2
Anti-metreleptin Antibody Positive	29	18	47
Neutralising	9	4	13
PL Subgroup Patients with Antibody Data	23	6	29
Anti-metreleptin Antibody Negative	2	0	2
Anti-metreleptin Antibody Positive	21	6	27
Neutralising	6	0	6

The potential impact of antibody formation on efficacy was investigated and is summarised in **Table 36**.

Table 36. Review of Potential Impact of Antidrug Antibodies on Efficacy during Metreleptin Treatment (NIH Studies 991265/20010769 and Study FHA101)

Impact on Efficacy	ADA Positive/ Neutralizing Positive				ADA Positive\Neutralizing Negative or ADA Negative			
	Total (N=38) N (%)	GL (N=25) N (%)	PL (N=13) N (%)	PL Subgroup (N=6) N (%)	Total (N=64) N (%)	GL (N=28) N (%)	PL (N=36) N (%)	PL Subgroup (N=23) N (%)
Positive[a]	14 (36.8)	9 (36.0)	5 (38.5)	4 (66.7)	41 (64.1)	23 (82.1)	18 (50.0)	14 (60.9)
Attenuated[b]/ worsened[c]	19 (50.0)	13 (52.0)	6 (46.2)	2 (33.3)	19 (29.7)	5 (17.9)	14 (38.9)	6 (26.1)
Transient[d]	12 (31.6)	8 (32.0)	4 (30.8)	2 (33.3)	NA	NA	NA	NA
Non-transient[e]	7 (18.4)	5 (20.0)	2 (15.4)	0 (0.0)	NA	NA	NA	NA
No improvement from baseline	0	0	0	0	3 (4.7)	0	3 (8.3)	2 (8.7)
Indeterminate[f]	5 (13.2)	3 (12.0)	2 (15.4)	0	1 (1.6)	0	1 (2.8)	1 (4.3)

Abbreviations: ADA = antidrug antibody; HbA1c = hemoglobin A1c; GL = generalised lipodystrophy; NA = not applicable; NAc = neutralizing activity; PL = partial lipodystrophy

[a] Denotes sustained improvement from baseline of HbA1c and triglycerides during metreleptin treatment.

[b] Typically denotes improvement and then decline of both HbA1c and triglyceride levels. May also apply when one parameter is within normal limits at baseline and remains low, but the other parameter becomes elevated over time to a clinically meaningful level associated with potential deleterious effects such as acute pancreatitis, or if sustained could lead to microvascular and macrovascular complications associated with poor glycemic control. Metabolic disturbance is usually temporally associated with the period of neutralizing activity (if applicable). Potential confounding factors such as compliance issues are considered when making this determination.

[c] Denotes decline from baseline in both HbA1c and triglycerides on treatment.

[d] Refers to an improvement or return to baseline level of metabolic parameters following attenuation/worsening associated with NAc. Note that this analysis was not applicable for neutralizing negative groups.

[e] Refers to lack of improvement or return to baseline level of metabolic parameters following attenuation/worsening associated with NAc. Note that this analysis was not applicable for neutralizing negative groups.

[f] Refers to divergent HbA1c and triglycerides results, but without elevation of the rising parameter sufficient to qualify for attenuated efficacy, as in (b) above also used in cases where worsening of disease was seen and non-compliance during this same time was known.

Limited information is available with regards to the reversibility following cessation of treatment. The only patient that had continued Nab seropositivity after study termination, and for whom data was available, was a GL patient.

Sixteen (42.1%) of a total of 38 patients whom developed nABs did not achieve resolution of NAc while receiving metreleptin or in the follow-up period.

In the PL group, 13 patients whom developed nABs during the metreleptin therapy, and 6 of them saw resolution of the NAc during the treatment itself. Of the 13 patients with NAbs only 5 had no impact whatsoever on efficacy.

In the GL group, 15 of the 25 patients that developed nABs had resolution of neutralising activity during treatment and in total 20 out of these 25 patients saw attenuation of efficacy. In the 10 GL patients that had no resolution of NAc, only four had unaffected efficacy.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of Efficacy for trial NIH 991265/20010769

Title: Long Term Efficacy and Safety of Leptin Replacement in the Treatment of Patients with Lipodystrophy			
Study identifier	991265 (pilot) and 20010769 (long-term)		
Design	Open-label, single-arm, single-centre, investigator-sponsored, phase 2/3		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 months (pilot) 12 months (long-term) Eligibility study & baseline assessments 7 days Extension on annual basis possible
Hypothesis	Superiority vs baseline		
Treatment (sub)groups	GL		Patients with generalized lipodystrophy (FAS – 62 patients)
	PL subgroup[a]		Patients with partial lipodystrophy and with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L (FAS with exclusion patient 901-080 – 29 patients)
Endpoints and definitions	Co-Primary endpoint	HbA1c	actual change from baseline in HbA1c at Month 12 (%)
	Co-Primary endpoint	Fasting TG	percent change from baseline in fasting serum triglycerides at Month 12 (mmol/L)
	Key secondary endpoint	FPG	Actual (and percent change – not in table) from baseline in fasting plasma glucose levels at Month 12 (mmol/L)
	Key secondary endpoint	Responder 1	≥1% decrease in HbA1c or ≥30% decrease in fasting serum triglycerides at Month 12 (%)
	Key secondary endpoint	Responder 2	≥1,5% decrease in HbA1c or ≥35% decrease in fasting serum triglycerides at Month 12 (%)
	Key secondary endpoint	Responder 3	≥2% decrease in HbA1c or ≥40% decrease in fasting serum triglycerides at Month 12 (%)
	Secondary endpoint	TC	Actual (and percent change – not in table) from baseline in total cholesterol through Month 12 (mmol/L)
	Secondary endpoint	LDL-C	Actual (and percent change - not in table) from baseline in LDL cholesterol through Month 12 (mmol/L)
	Secondary endpoint	ALT/AST	Actual change from baseline in ALT and AST at each post-baseline visit through Month 12 (U/L)
Database lock	19/12/2014		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	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				
Descriptive statistics and estimate variability	Treatment group		BL GL	Month 12 GL	BL subgroup[a]	Month 12 PL subgroup[a]
	Number of subjects		62	62	29	29
	Mean HbA1c (SD)		8.6 (2.33)	6.4 (1.68)	8.8 (1.91)	8.0 (1.83)
	Mean fasting TG (SD)		14.7 (25.66)	4.5 (6.10)	15.7 (26.42)	6.0 (8.41)
	Mean FPG (SD)		10.2 (5.05)	7.0 (3.40)	10.0 (4.36)	8.1 (3.55)
	Mean TC (SD)		5.9 (3.66)	3.9 (1.30)	6.4 (2.80)	5.6(2.21)
	Mean LDL-C (SD)		2.6 (1.35)	2.0 (0.81)	2.8 (1.02)	2.8 (0.77)
	Mean ALT/AST (SD)		111.9 (112.62)/ 75.0 (71.07)	76.3 (160.24)/ 63.1 (143.35)	39.2 (28.02)/ 31.9 (19.64)	34.5 (22.94)/ 25.8 (13.15)
Effect estimate per comparison	Primary endpoints	Comparison groups		BL vs 12 months therapy in GL	BL vs 12 months therapy in PL subgroup[a]
	HbA1c	Mean actual change from BL (SD)		-2.2 (2.15)	-0.9 (1.23)
		[95% CI]		[-2.7,-1.6]	[-1.4,-0.4]
		P-value (paired t-tests)		<0.001	<0.001
	Fasting TG	Mean % change from BL (SD)		-32.1 (71.28)	-37.4 (30.81)
		[95% CI]		[-51.01,-13.2]	[-49.6,-25.2]
		P-value (paired t-tests)		0.001	<0.001
	Secondary endpoints	Comparison groups		BL vs 12 months therapy in GL	BL vs 12 months therapy in PL subgroup
	FPG	Mean actual change from BL (SD)		-3.0 (4.72)	-1.8 (2.83)
		[95% CI]		[-4.2,-1.7]	[-2.9,-0.7]
		P-value (paired t-tests)		<0.001	0.003
	Responder 1	n/N (%)		79.9	67.9
		[95% CI][b]		[67.2,89.0]	[47.7,84.1]
	Responder 2	n/N (%)		74.6	50.0
		[95% CI][b]		[61.6,85.0]	[30.7,69.4]
	Responder 3	n/N (%)		66.1	42.9
		[95% CI][b]		[52.6,77.9]	[24.5,62.8]
	TC	Mean actual change from BL (SD)		-2.3 (2.91)	-0.9 (1.52)
	LDL-C	Mean actual change from BL (SD)		-0.9 (1.29)	-0.3 (0.66)
	ALT/AST	Mean actual change from BL (SD)		-53.1 (126.6)/ -23.8 (142.38)	-5.0 (11.95)/ -6.0 (14.77)

Notes	month 12 = month 12 or LOCF [a] One patient was excluded from the analysis of the FAS due to >1000% increase from b**a**seline to Month 12 for triglyceride levels (only patient in the study with this level of change at Month 12: entered the trial with a triglyceride level of 3.0 mmol/L, which increased to 18.6 mmol/L at Month 6 and to 37.7 mmol/L at Month 12. This patient was terminated from the study by the Investigator 2 days prior to the Month 12 assessment for noncompliance with study drug administration. [b] based on 2-sided exact binomial proportions			
Analysis description	Sensitivity / supportive analyses based on the CFAS, EEAS, and CEEAS.			
Analysis population and time point description	CFAS: Controlled Concomitant Medication FAS, all patients in the FAS who have controlled concomitant medication use, described as no change or a decrease in baseline concomitant medications (anti-diabetic or lipid lowering therapies), prior to Month 12 EEAS: Efficacy Evaluable Analysis Set, patients in the FAS who have either efficacy parameter of interest measured at Month 12 and have no major protocol violations prior to Month 12 CEEAS: all patients in the CFAS who have either efficacy parameter of interest measured at Month 12 and have no major protocol violations prior to Month 12			
Effect estimate per comparison	CFAS - Primary endpoints	Comparison groups	BL vs 12 months therapy in GL	BL vs 12 months therapy in PL subgroup
		Number of subjects	54	23
	HbA1c	Mean actual change from BL (SD)	-1.9 (1.81)	-0.7 (0.69)
		[95% CI]	[-2.6, -1.2]	[-1.2, -0.2]
		P-value (paired t-tests)	<0.001	0.008
	Fasting TG	Mean % change from BL (SD)	-26.5 (76.17)	-34.0 (31.44)
		[95% CI]	[-49.7, -3.3]	[-49.6, -18.3]
		P-value (paired t-tests)	0.026	<0.001
	EEAS - Primary endpoints	Comparison groups	BL vs 12 months therapy in GL	BL vs 12 months therapy in PL subgroup
		Number of subjects	38	19
	HbA1c	Mean actual change from BL (SD)	-2.2 (2.19)	-0.9 (1.45)
		[95% CI]	[-2.9, -1.5]	[-1.6, -0.2]
		P-value (paired t-tests)	<0.001	0.011
	Fasting TG	Mean % change from BL (SD)	-49.8 (42.14)	-41.3 (27.73)
		[95% CI]	[-63.9, -35.8]	[-54.7, -27.9]
		P-value (paired t-tests)	<0.001	<0.001
	CEEAS - Primary endpoints	Comparison groups	BL vs 12 months therapy in GL	BL vs 12 months therapy in PL subgroup
		Number of subjects	33	13
	HbA1c	Mean actual change from BL (SD)	-1.8 (1.75)	-0.5 (0.75)
		[95% CI]	[-2.6, -1.0]	[-1.4, 0.4]
		P-value (paired t-tests)	<0.001	0.194

	Fasting TG	Mean % change from BL (SD)	-46.6 (42.74)	-39.1 (25.43)
		[95% CI]	[-62.2, -30.9]	[-56.2, -22.1]
		P-value (paired t-tests)	<0.001	<0.001
Analysis description	Mixed-effect model repeated measures (MMRM analysis) for long-term efficacy based on FAS			
Effect estimate per comparison	Primary endpoints	Comparison groups	BL vs therapy in GL	BL vs therapy in PL subgroup
	HbA1c	LSmean change HbA1c	-1.4	-0.6
		P-value (paired t-tests)	<0.001	<0.001
	Fasting TG	LSmean % change from BL	-22.4	-18.6
		P-value (paired t-tests)	<0.001	=0.004

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

A total of 4 patients aged 2 to 6 years of age were treated in Study NIH 991265/20010769; all were female and all had congenital generalised lipodystrophy (CGL). Changes in the metabolic parameters in these patients following metreleptin treatment are summarised in **Table 38**.

Table 38. Change from baseline in HbA1c and fasting triglycerides in GL patients, 2-6 years of age treated with metreleptin, Study 991265/20010769

	HBA1c		Triglycerides		
Analysis Visit	Analyzed Value (%)	Change from Baseline (%)	Analyzed Value (mg/dL)	Change from Baseline (mg/dL)	% Change from Baseline
Baseline	4.9		193		
Month 12	5.0	0.1	299	106	54.7
Month 20	4.9	0.0	211	18	9.3
Month 36	4.8	-0.1	52	-141	-73.1
Baseline	5.3		268		
Month 12	5.3	0.0	81	-187	-69.8
Month 24	5.1	-0.2	338	70	26.1
Month 36	5.1	-0.2	296	28	10.4
Baseline	8.7		370		
Month 12	10.0	1.3	377	7	1.9
Month 42	8.4	-0.3	92	-278	-75.1
Baseline	4.5		200		
Month 12	4.4	-0.1	265	65	32.5
Month 20	4.5	0.0	145	-55	-27.5

Baseline metabolic parameters in these patients were also compared to those of the other paediatric populations in the study **Table 39**.

Table 39. Mean (range) baseline HbA1c, triglycerides and fasting plasma glucose in paediatric GL patients by age category, Study 991265/20010769-FAS

Baseline Level	Age Category		
	<6 Years	6 to <12 Years	12 to <18 Years
HbA1c			
n	5	12	26
Mean	5.7	6.4	9.7
Minimum, Maximum	4.5, 8.7	4.5, 8.4	5.6, 13.7
Triglycerides			
n	5	12	26
Mean	338.8	256.2	1609.2
Minimum, Maximum	193, 663	122, 724	49, 8229
Fasting Plasma Glucose			
n	5	12	26
Mean	106	120.5	207.6
Minimum, Maximum	64, 193	71, 234	73, 478

Supportive study

Study FHA101 was a treatment IND study designed to provide access to metreleptin for patients 5 years of age and older physician-confirmed lipodystrophy (GL and PL) who had diabetes mellitus and/or hypertriglyceridaemia with triglycerides >200 mg/dL.

Dosing was administered on a body weight basis. At the start of the study, patients initiated metreleptin at 0.02 mg/kg twice daily (BID) for 1 week, and increased the dose to 0.04 mg/kg BID for the rest of the treatment period unless dose adjustment was necessary. Following a protocol amendment, patients weighing ≤40 kg received the recommended daily dose of 0.06 mg/kg metreleptin and patients weighing >40 kg, the recommended daily dose was 2.5 mg for males and 5.0 mg for females. Metreleptin was to be administered once daily (QD) following this amendment. Based on clinical response (e.g., inadequate metabolic control or excessive weight loss or tolerability issues), metreleptin dose may have been adjusted in increments or decrements of 0.02 mg/kg for patients ≤40 kg and 1.25 to 2.5 mg for patients >40 kg.

This study is enrolled a total of 41 patients. As the initial purpose of this treatment IND study was descriptive, no statistical inferences were planned.

Nine (9) of the 41 patients had GL and 32 had PL. Among the GL patients, 2 had CGL, 6 had AGL, and for 1 patient the type of GL was not reported. Most patients with PL had the familial form (29 patients); 3 patients had APL.

Among the 9 patients with GL included in the FAS, mean HbA1c was reduced from 7.7% at baseline (n=9) to 6.2% at Month 12/LOCF (n=5), a mean change across patients of -1.2%. In addition, metreleptin treatment led to improvements in mean fasting triglyceride concentrations in patients with GL. Mean fasting triglyceride concentrations were reduced from 19.9 mmol/L at baseline (n=8) to 7.6 mmol/L at Month 12/LOCF (n=6), corresponding to a mean percent change across patients of -26.9%.

Among the 7 patients in the PL subgroup included in the FAS, mean HbA1c was reduced from 7.8% at baseline (n=7) to 7.0% at Month 12/LOCF (n=7), a mean change of -0.8%. Mean triglyceride concentrations were lower in this group of patients compared to those with GL. In the PL subgroup,

mean triglyceride concentrations were reduced from 4.0 mmol/L at baseline (n=7) to 3.6 mmol/L at Month 12/LOCF (n=7), a mean change of -8.5%.

Although reductions were observed for both HbA1c and triglycerides to Month 12/LOCF in both the overall GL group and the PL subgroup, none of the changes reached statistical significance.

Analyses that assessed target reductions in HbA1c and triglycerides also showed that patients derived benefit from treatment with metreleptin. Overall, 3 (50%) of 6 patients in the FAS with GL had a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with the same number achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides at that time. In the PL subgroup for the FAS, 2 (29%) of the 7 patients achieved a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 1 patient (14%) achieving the highest target decreases of ≥2% in HbA1c or ≥40% in triglycerides.

Reductions were observed in transaminase levels during metreleptin treatment. Mean change in ALT in the GL group from baseline to Month 12/LOCF was -191.5 U/L and in AST was -104.1 U/L. In the PL subgroup, who had lower baseline levels of ALT and AST, mean changes to Month 12/LOCF were -5.1 U/L and -0.3 U/L, respectively.

In this study serum leptin levels were not set among entry criteria (declared to be below 12ng/mL), and were measured during the study. In GL patients, mean and median increases from baseline in leptin concentrations at Month 3 (n=3) were 0.1 ng/mL and 0 ng/mL, respectively, at Month 6 (n=2) were 56.5 ng/mL and 56.5 ng/mL, respectively; and at Month 12 (n=3) were 59.2 ng/mL and 1.0 ng/mL, respectively.

In the PL subgroup, mean and median increases from baseline in leptin concentrations at Month 3 (n=4) were 103.1 ng/mL and 94.9 ng/mL, respectively, at Month 6 (n=4) were 502.8 ng/mL and 320.4 ng/mL, respectively, and at Month 12 (n=4) were 650.5 ng/mL and 144.6 ng/mL, respectively.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study NIH 991265/20010769 and Study FHA101 were designed as open-label single-arm studies. Given the rarity of the disease and the lack of therapeutic options specific for the treatment of LD, the single-arm, open-label design was considered appropriate. Utilising a placebo control in this patient population at risk for serious, life-threatening metabolic complications after marked improvements with metreleptin were demonstrated in the initial pilot study was considered not justifiable based on ethical considerations. In addition, the studies' efficacy endpoints are objective measurements, including HbA1c, triglycerides and plasma glucose levels, and thus treatment effects can be appropriately evaluated with a single-arm (baseline-controlled, within patient) design.

In these studies there was a possibility to increase or decrease the dose based on inadequate control of metabolic parameters or tolerability issues / intolerable weight loss. Because of the wide range of variation in the clinical presentation of patients, it was not possible to define predetermined thresholds of metabolic parameters that would appropriately guide dose modifications. Best clinical judgment was used to make dose modifications based on the constellation of metabolic and clinical data available for each patient.

In accordance with the practice in the clinical development programme, the product information stipulates that 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 of 0.13 mg/kg in patients weighing ≤40 kg and 10 mg for those weighing > 40kg. 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 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.

Metreleptin dose increases in adults and children based on incomplete clinical response can be considered after a minimum of 6 months of treatment, allowing for lowering concomitant insulin, oral anti-diabetic and/or lipid lowering medication.

As an analogue of leptin, it was anticipated that metreleptin would improve the metabolic abnormalities associated with leptin deficiency in patients with lipodystrophy, i.e., reduce HbA1c and triglycerides. In view of the role these metabolic abnormalities have in the morbidity and mortality associated with LD and given the expected effect of metreleptin, changes in HbA1c and triglycerides were the co-primary efficacy variables. This is consistent with the Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005), that the primary efficacy endpoint is a surrogate endpoint that is clinically relevant to the patient and the progression of disease.

Efficacy data and additional analyses

Analysis of the results at 12 months after initiation of treatment was considered appropriate as metreleptin is intended to treat a chronic disease; this time period would allow for individual dose titration to achieve maximum effect in a given patient and an acceptable time frame over which to assess the clinical impact of the treatment. In order to account for patients who may have discontinued treatment prior to that time and to account for differences in the availability of patients to attend study centre visits due to significant travel (i.e., for patients outside the country), LOCF methods were used for determination of changes from baseline to Month 12. Specifically, samples for HbA1c and triglycerides obtained on or after Day 180 were used in the analysis for patients who did not have samples obtained within the Month 12 window (Day 365 ±65 days).

The primary efficacy analyses 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).

The applicant defined a sub-group of patients with PL for analysis who appear to have clinically similar metabolic disturbances as patients with GL and who could equally benefit from metreleptin treatment. This subset included patients with baseline HbA1c ≥6.5% and/or triglycerides ≥500 mg/dL.

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

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

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

Furthermore, clinically meaningful and statistically significant improvements in hypertriglyceridaemia were also reported:

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

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

Reductions in HbA1c and triglycerides were sustained over long-term treatment in patients with GL and in the PL subgroup. Most patients received 2 or more years of therapy with a maximum duration of 14 years; total patient-years of exposure across the LD studies was >500 years. Based on the results of the MMRM analysis, which takes into account changes over all visits, statistically significant reductions from baseline were observed in both HbA1c and triglycerides in patients with GL and in the PL subgroup in Study NIH 991265/20010769. Results for the MMRM analysis were directionally consistent but not statistically significant in Study FHA101.

Target responses of ≥1% in HbA1c and/or ≥30% in triglycerides were observed in patients with GL and in the PL subgroup.

In Study NIH 991265/20010769, nearly 80% of GL patients and 68% of patients in the PL subgroup had a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF with 66% and 43%, respectively, achieving the highest target decreases of ≥2% in HbA1c or a ≥40% in triglycerides.

Patients in the supportive study also achieved these target decreases with 3 of 6 GL patients and 2 of 7 patients in the PL subgroup having a ≥1% actual decrease in HbA1c or a ≥30% decrease in triglycerides at Month 12/LOCF.

No robust conclusions could be drawn with regards to the levels of baseline HbA1c and triglycerides used to define the PL sub-group in need of treatment with metreleptin. The applicant-proposed a cut-off level for HbA1c of 6.5%, in which a greater reduction in HbA1c was seen in patients compared to the overall group of patients with PL. Further subgroup analyses by baseline metabolic abnormalities showed that a meaningful difference in efficacy results was related to the patient's baseline level of HbA1c or triglycerides. Patients with more abnormal results had greater decreases from baseline in these parameters.

However, due to the very low number of analysed patients the CHMP considered that in this rare condition, patients should be treated with metreleptin if adequate metabolic control had not been achieved by standard treatments. At the same time it was acknowledged that stipulating strict thresholds on metabolic parameters would not be the best way to define the target population especially since the limited dataset available, does not allow determining these with any precision.

Study NIH 991265/20010769 also included specific eligibility criteria for leptin levels (<12 ng/mL for females and <8 ng/mL for males >5 years). In study FHA10, the PL sub-group definition required patients to have leptin levels <12 ng/mL. Based on these inclusion criteria the initially applied indication in partial lipodystrophy, was proposed to be restricted to patients with leptin levels <12 ng/ml. The Multi-Society Practice Guideline (MPSG, Brown, 2016 J Clin Endocrinol Metab) considers

that metreleptin may be considered in severely hypoleptinaemic patients with leptin levels <4 ng/mL.

The CHMP noted that 2 of the 3 studies upon which the MPSG guidelines are based upon, conclude that changes in, HbA1c and triglycerides were not significantly related to baseline leptin levels (Vatier 2015 and Simha 2012). Only the third study, Diker-Cohen (2015), concluded that metreleptin was effective in all PL subgroups except those with baseline triglycerides 500 mg/dL, HbA1c 8% or endogenous leptin 4 ng/mL. In addition, sub-group analyses conducted by the applicant did not demonstrate statistical significant differences between patients with different baseline leptin levels in the reduction in HbA1c or in the levels of triglycerides. Patients in the 4-12 ng/ml range achieved an even slightly better improvement of their HbA1C and TG values in both the MSPG and the Applicant defined groups, although no robust conclusions can be made due to the low numbers in the analysed subsets. Based on the above and the fact that endogenous leptin levels in PL patients are known to be age and gender dependant the CHMP concluded that use of metreleptin in PL should not be determined by baseline leptin levels.

Therefore the CHMP considered that the appropriate target population for treatment with metreleptin in patients with partial LD was confirmed familial partial LD or acquired partial LD (*Barraquer-Simons syndrome*), for whom standard treatments have failed to achieve adequate metabolic control.

Results on primary endpoints were less pronounced in children < 6 years, which could be due to the low metabolic baseline values in these patients as HbA1c values were in the normal range patents <6 years (5.7%) and lower in patients ≥6 to <12 years (6.4%) compared to the older age groups (9.7% and 9.1%). Mean decreases from baseline to month 12/LOCF in triglycerides for the GL group were noted in all age groups with larger mean changes observed in the 2 older age groups (-42.9% and -35.3%) compared to the younger age groups (-10.5% and -14.1%). This consistent trend in these parameters is in accordance with what is known about the natural history of GL whereby the severity of disease in inadequately treated GL patients worsens over time. Therefore and despite the small treatment effect of metreleptin in these very children, the CHMP considered that the GL indication should include children 2 years of age and above as early treatment in these young patients could potential prevent or delay avoid onset of complications.

Regarding the PL population, there are no data available for patients under 12 years, and only 5 patients were analysed in the age group 12-18 years. This is possibly a consequence of the fact that PL diagnosis is normally established later. Given the complete lack of data but also the safety concerns over formation of antibodies against endogenous leptin, the CHMP considered that for the PL indication patients less than 12 years of age should be excluded.

In common with other products of this type, there is a concern regarding the formation of neutralising ADA which in this case could potentially bind on metreleptin but also against endogenous leptin (especially in PL patients). Currently there is no method available which would allow for a distinction between the two.

Sixteen (42.1%) of a total of 38 patients whom developed NABs did not achieve resolution of NAc while receiving metreleptin or in the follow-up period. In the PL group, 13 patients whom developed NAbs during the metreleptin therapy, and 6 of them saw resolution of the NAc during the treatment itself. Of the 13 patients with NAbs only 5 had no impact whatsoever on efficacy. In the GL group, 15 of the 25 patients that developed NAbs had resolution of neutralising activity during treatment and in total 20 out of these 25 patients saw attenuation of efficacy. In the 10 GL patients that had no resolution of NAc, only four had unaffected efficacy.

Generally, there were no clear differences between the patient subtypes regarding NAb impact on efficacy or resolution. Even though available data raise concerns about reversibility of NAb formation

during metreleptin treatment it should be noted that no patient saw a total failure in efficacy, and it is expected that up-titration of the dose should be able to deal with any efficacy attenuation problems. Moreover, it should be noted that about half of the NAb seropositive subjects became seronegative again during treatment, and that as of today no total losses in efficacy have been noted. This coupled with the fact that 2 out of three Nab seropositive subjects that had data post-treatment available also had resolution of their seropositive status suggests that any possible impact, on endogenous leptin activity is likely transient.

The CHMP considered that currently there are not enough data to conclude on the reversibility of NAc after cessation of therapy and thus on any potential impact on endogenous leptin activity. The analysis is further complicated by the fact that with the new receptor binding assay, the majority of patients were reported as having some kind of blocking activity. Loss of efficacy, potentially due to Nabs is therefore included in the RMP. The applicant will employ an immunogenicity strategy to further test anti-drug antibodies in the future, which will help elucidate any potential clinical significant effects of antibody formation. This will include, a revalidation of the ADA binding assay, standardising the antibody used in the ADA Binding Assay and ECLIA Receptor Binding Assays and standardising the antibody used in the ADA Binding Assay and ECLIA Receptor Binding Assays and development of a Mass spectroscopy technique to differentiate endogenous leptin and metreleptin. These techniques will be used in a planned open label study in PL patients

Additional efficacy data needed in the context of a MA under exceptional circumstances

Taking into account the totality of the available data, the CHMP was of the view that the data set on the clinical efficacy of Myalepta under normal conditions of use could not be considered comprehensive as due to the rarity of the studied conditions and heterogeneity of the patients included in the target population, active or placebo controlled studies of sufficient size are not feasible. Due to these limitations it is not possible to determine the effect of baseline levels of metabolic parameters on the treatment effect.

In addition, due to technical limitations it is not possible to distinguish between the effect of anti-drug antibody formation and antibodies against endogenous leptin which could impact the efficacy of the product.

The CHMP was therefore of the view that a marketing authorisation under exceptional circumstances should be granted subject to a number of obligations, including a disease registry in order to evaluate the long-term effectiveness of treatment with Myalepta under conditions of routine clinical care.

In addition, the results of an open label study will be submitted in order to provide further information on the effect of metreleptin in patients with PL on poor metabolic control once background therapy has been maximised.

2.5.4. Conclusions on the clinical efficacy

A clear effect on HbA1c and triglyceride levels has been demonstrated for metreleptin from the data submitted in patients with GL and PL. Therefore, it was concluded that metreleptin is an effective treatment option for patients with congenital or acquired generalised lipodystrophy and familial or acquired partial lipodystrophy for whom standard treatments have failed to achieve adequate metabolic control.

However due to the small number of patients investigated and the lack of control, available data are not considered sufficient to fully characterise the magnitude of effect which can be affected by concomitant medications commonly used in these conditions .

The CHMP thus considered that the available data set on the clinical efficacy was not comprehensive and that the following measures would be necessary to generate additional efficacy data in the context of a marketing authorisation under exceptional circumstances:

- A lipodystrophy registry, to evaluate long term effectiveness of treatment with metreleptin
- An open label study to further characterise the effect of metreleptin on poor metabolic control

2.6. Clinical safety

Patient exposure

Safety data in support of this application was from two trials in LD, one of which was initiated by a third party (the US NIH) and consisted of two distinct trials that were pooled and analysed as one. The other trial was a smaller complementary sponsor initiated trial, FHA101. Both of these trials were open-label, non-controlled PhII trials that included all major forms of LD (AGL, CGL, FPL, APL).

A total of 148 patients were included in the safety analysis in the LD trials and 138 from the post-marketing setting.

A breakdown of the types of patients in each LD study is provided in **table 40.**

Table 40. Numbers of patients included in LD studies, by lipodystrophy type

	CGL	AGL	PL subgroup	Overall PL
NIH991265/20010769	45 (68% of overall GL)	21 (32% of overall GL)	31 (87% FPL, 13 APL)	41 (85% FPL, 15% APL)
FHA101	2 (25% of overall GL)	6 (75% of overall GL)	7 (86% FPL, 14% APL)	32 (91% FPL, 9% APL)

AGL: acquired generalised lipodystrophy, CGL: congenital partial lipodystrophy, FPL: familial partial lipodystrophy, APL: acquired partial lipodystrophy

For the safety analysis the outcomes were not pooled due to differences in study design and population makeup. The exception to this was the analysis of immunogenic events, as differences in immunogenic potential were considered unlikely between populations.

Additionally, supportive safety data was extracted from 5 PhII trials in obese patients (two of which recruited explicitly diabetic patients) which were all placebo-controlled. Though the indication, trial design and patient morbidity are wildly different from the LD trials, the placebo-controlled nature of the trials can be considered to have some informative value on possible treatment relatedness of events noted in the LD trials.

The 5 analysed obesity studies included a total of 632 patients whom received metreleptin at least once, and 236 patients on placebo treatment. Of these 868 patients 296 were subjects suffering from type 2 diabetes. Of the 632 metreleptin patients 199 were on a dose of 10 mg, and 433 were on a dose of 20 mg.

Across all of the 7 trials mentioned above 1476 patients have been given metre leptin at least once, and of those 1113 received metreleptin at least once in monotherapy.

In the NIH study the total amount of exposure in patient years for GL patients was 328.3 years with a mean overall exposure duration of 62.5 months and a mean daily dose of 5.0 mg/day. In the PL subgroup and overall PL group this was 121.3 and 162 years respectively with respective mean overall exposure durations of 47.5 and 48.1 months with mean daily doses of 8.4 mg/day (high dose mainly driven by subgroup patients), again respectively.

In the FHA101 study the total exposure in patient years was 11.3 for GL patients and 61.9 for PL patients (28.4 in the subgroup). This correlated with mean average daily doses of 3.1, 7.6 and 8.9 respectively (due to the relative lower number of subgroup patients versus the overall number of PL patients the dose in the latter group was less driven by the former). The mean overall durations of exposure on a patient level were 25.9, 27.8 and 49.4 months respectively.

In the obesity studies the median duration of exposure to metreleptin was 12.4 weeks and to placebo 16.0 weeks (with a maximum of 40 weeks 40 weeks). Median duration of exposure was somewhat higher in the obesity studies in subjects with Type 2 diabetes (16.1 and 16.0 weeks in the metreleptin and placebo groups, respectively) compared to the obesity studies in subjects without diabetes (12.0 and 14.1, respectively).

Most subjects in the Obesity Studies Pool, including 421 (54%) of 784 who received metreleptin and had exposure data available and 220 (63%) of 351 who received placebo, were exposed to study treatment for >12 weeks with ~20% of subjects in both groups receiving treatment for >24 weeks.

There was no apparent difference in duration of exposure to metreleptin for subjects who received 10 mg or 20 mg in either group of studies (with or without diabetes).

Adverse events

Table 41, Table 42 and **Table 43** provide a concise summary of the TEAE rates seen in the NIH, FHA101 and pooled supportive obesity studies respectively.

Table 41. Overall Summary of TEAEs (NIH study, Safety Analysis Set)

Patients with at Least One:	Generalised Lipodystrophy			Partial Lipodystrophy	
	Males (N=15)	Females (N=51)	Overall (N=66)	PL Subgroup[A] (N=31)	Overall (N=41)
TEAE	13 (86.7)	46 (90.2)	59 (89.4)	27 (87.1)	35 (85.4)
Drug-Related TEAE	4 (26.7)	28 (54.9)	32 (48.5)	7 (22.6)	8 (19.5)
Severe TEAE	6 (40.0)	23 (45.1)	29 (43.9)	13 (41.9)	16 (39.0)
Drug-Related Severe TEAE	0	7 (13.7)	7 (10.6)	0	0
Treatment-emergent SAE	4 (26.7)	19 (37.3)	23 (34.8)	7 (22.6)	10 (24.4)
Drug-Related Treatment-emergent SAE	0	3 (5.9)	3 (4.5)	0	0
TEAE Leading to Study Drug Discontinuation	0	5 (9.8)	5 (7.6)	1 (3.2)	1 (2.4)
On-Study Deaths	0	3 (5.9)	3 (4.5)	1 (3.2)	1 (2.4)

Abbreviations: HbA1c = haemoglobin A1c; PL = partial lipodystrophy; 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.

Table 42. Overall Summary of TEAEs (Study FHA101, Safety Analysis Set)

Patients with at Least One:	Generalised Lipodystrophy Overall (N=9)	Partial Lipodystrophy	
		PL Subgroup[A] (N=7)	Overall (N=32)
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)

Abbreviations: HbA1c = haemoglobin A1c; PL = partial lipodystrophy; SAE = serious adverse event; TEAE = treatment-emergent adverse event

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

Table 43. Overall Summary of TEAEs (supportive obesity studies, Safety Analysis Set)

	Obese Subjects (N=776) Studies 970164, 970213, and 908236				Obese Subjects with Type 2 Diabetes (N=296) Studies 970171 and 970188				Overall	
	Placebo	Metreleptin			Placebo	Metreleptin				
At Least One:	(N=251) n (%)	10mg (N=214) n (%)	20mg (N=374) n (%)	Overall (N=588) n (%)	(N=100) n (%)	10mg (N=61) n (%)	20mg (N=135) n (%)	Overall (N=196) n (%)	Placebo (N=351) n (%)	Metreleptin (N=784) n (%)
TEAE	208 (82.9)	192 (89.7)	354 (94.7)	546 (92.9)	92 (92.0)	53 (86.9)	125 (92.6)	178 (90.8)	300 (85.5)	724 (92.3)
Treatment-related TEAE	96 (38.2)	171 (79.9)	313 (83.7)	484 (82.3)	58 (58.0)	42 (68.9)	97 (71.9)	139 (70.9)	154 (43.9)	623 (79.5)
Severe TEAE	11 (4.4)	9 (4.2)	21 (5.6)	30 (5.1)	9 (9.0)	3 (4.9)	11 (8.1)	14 (7.1)	20 (5.7)	44 (5.6)
Life-threatening TEAE	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	3 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	1 (0.1)
SAE	6 (2.4)	3 (1.4)	3 (0.8)	6 (1.0)	7 (7.0)	3 (4.9)	6 (4.4)	9 (4.6)	13 (3.7)	15 (1.9)
TEAE resulting in treatment discontinuation	8 (3.2)	14 (6.5)	48 (12.8)	62 (10.5)	12 (12.0)	6 (9.8)	10 (7.4)	16 (8.2)	20 (5.7)	78 (9.9)
Death on study	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event
Note: Of the 776 unique obese subjects, 63 received metreleptin followed by randomisation to placebo (Study 970213) and therefore are represented in both the placebo and 20 mg metreleptin treatment groups for the corresponding treatment period.

An overview of treatment-related events occurring in more than 1 patient in the LD studies or more than 1% in the supportive obesity studies is given in **Table 44, Table 45** and **Table 46**respectively.

Table 44. Patient Incidence for Drug-Related TEAEs Reported in >1 Patient in the Overall GL or PL Groups (NIH study, Safety Analysis Set)

	Generalised Lipodystrophy			Partial Lipodystrophy	
MedDRA Preferred Term	Males (N=15) n (%)	Females (N=51) n (%)	Overall (N=66) n (%)	PL Subgroup[A] (N=31) n (%)	Overall (N=41) n (%)
Weight decreased	3 (20.0)	12 (23.5)	15 (22.7)	1 (3.2)	1 (2.4)
Hypoglycaemia	1 (6.7)	7 (13.7)	8 (12.1)	3 (9.7)	3 (7.3)
Decreased appetite	0	4 (7.8)	4 (6.1)	0	0
Fatigue	1 (6.7)	3 (5.9)	4 (6.1)	3 (9.7)	3 (7.3)
Neutralising antibodies	0	4 (7.8)	4 (6.1)	0	0
Alopecia	0	2 (3.9)	2 (3.0)	2 (6.5)	2 (4.9)
Injection site reaction	0	2 (3.9)	2 (3.0)	1 (3.2)	2 (4.9)
Menorrhagia	0	2 (3.9)	2 (3.0)	0	0
Nausea	0	2 (3.9)	2 (3.0)	0	0

Abbreviations: GL = generalised lipodystrophy; HbA1c = haemoglobin A1c; MedDRA = Medical Dictionary for Regulatory Activities; PL = partial lipodystrophy

Table 45. Patient Incidence for drug -related TEAEs Reported in > 1 Patient in the Overall GL or PL Groups (FHA101 study, Safety Analysis Set)

	Generalised Lipodystrophy			Partial Lipodystrophy	
MedDRA Preferred Term	Males (N=1) n (%)	Females (N=8) n (%)	Overall (N=9) n (%)	PL Subgroup[A] (N=7) n (%)	Overall (N=32) n (%)
Weight decreased	1 (100)	0	1 (11.1)	0	1 (3.1)
Hypoglycaemia	0	2 (25.0)	2 (22.2)	2 (28.6)	8 (25.0)
Muscle Spasms	0	0	0	0	2 (6.3)
Headache	0	0	0	1 (14.3)	3 (9.4)
Injection site reaction	0	4 (50.0)	4 (44.4)	3 (42.8)	11 (34.3)
Nausea	0	0	0	2 (28.6)	8 (25.0)
Abdominal Pain	1 (100.0)	0	1 (11.1)	1 (14.3)	1 (3.1)

Abbreviations: GL = generalised lipodystrophy; HbA1c = haemoglobin A1c; MedDRA = Medical Dictionary for Regulatory Activities; PL = partial lipodystrophy

Table 46. Common (Incidence ≥1%) treatment-related TEAEs in the Obesity Studies Pool (Safety Analysis Set)

	Obese Subjects (N=776) Studies 970164, 970213, and 908236				Obese Subjects with Type 2 Diabetes (N=296) Studies 970171 and 970188				Overall	
	Placebo	Metreleptin			Placebo	Metreleptin				
MedDRA Preferred Term	(N=251) n (%)	10mg (N=214) n (%)	20mg (N=374) n (%)	Overall (N=588) n (%)	(N=100) n (%)	10mg (N=61) n (%)	20mg (N=135) n (%)	Overall (N=196) n (%)	Placebo (N=351) n (%)	Metreleptin (N=784) n (%)
Injection site reaction	75 (29.9)	166 (77.6)	306 (81.8)	472 (80.3)	53 (53.0)	38 (62.3)	95 (70.4)	133 (67.9)	128 (36.5)	605 (77.2)
Headache	6 (2.4)	11 (5.1)	15 (4.0)	26 (4.4)	1 (1.0)	0 (0.0)	2 (1.5)	2 (1.0)	7 (2.0)	28 (3.6)
Fatigue	6 (2.4)	6 (2.8)	11 (2.9)	17 (2.9)	0 (0.0)	1 (1.6)	2 (1.5)	3 (1.5)	6 (1.7)	20 (2.6)
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.0)	7 (11.5)	7 (5.2)	14 (7.1)	3 (0.9)	14 (1.8)
Nasopharyngitis	3 (1.2)	7 (3.3)	5 (1.3)	12 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	12 (1.5)
Urticaria	1 (0.4)	2 (0.9)	9 (2.4)	11 (1.9)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.5)	1 (0.3)	12 (1.5)
Nausea	5 (2.0)	2 (0.9)	6 (1.6)	8 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.4)	8 (1.0)
Pyrexia	1 (0.4)	1 (0.5)	6 (1.6)	7 (1.2)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.3)	8 (1.0)

Abbreviations: MedDRA = medical dictionary for regulatory activities
Note: Of the 776 unique obese subjects, 63 received metreleptin followed by randomisation to placebo (Study 970213) and therefore are represented in both the placebo and 20 mg metreleptin treatment groups for the corresponding treatment period.

Serious adverse event/deaths/other significant events

SAEs

A high proportion of patients in the LD studies reported SAEs (35% NIH-GL, 23% NIH-PLsbg, 30% NIH-PL, 67% FHA-GL, 0% FHA-PLsbg, 40% FHA-PL), but only few events were reported in more than one person, including abdominal pain and pancreatitis, pneumonia, sepsis, worsening underlying liver disease and cardiac failure in the NIH study and liver test elevated and hypoglycaemia in the FHA101 study.

In the NIH study only 3 SEAs, all in the GL patients, were considered as drug-related. It concerned cases of hypertension, respiratory distress and anaplastic large-cell lymphoma (ALCL) in one patient each. Of special interest was the ALCL case, given that T-cell lymphomas are AEs of special consideration, in which the patient developed ALCL 10 months after having been found positive for NAbs. Treatment was interrupted for 6 months, the neoplasm was excised, treatment was restarted and the patient remained neoplasm free for the rest of her study participation duration.

In the FHA101 study the only treatment-related TESAEs that affected more than one patient and was considered drug-related occurred in the non-subgroup PL patients, namely hypoglycaemia ad rata of 8%. Hypoglycaemic potential is a known and identified risk of metreleptin treatment and addressed in the SmPC.

Over all 5 obesity studies a slightly higher incidence of SAEs was observed in the placebo group than in the metreleptin group. In total 2% of 784 subjects who received metreleptin and 4% of 351 subjects who received placebo reported at least 1 SAE and no SAEs had an incidence of more than 2

subjects. Treatment-related SAEs included injection site reaction and asthma in 1 subject who received metreleptin, chest pain and hypertension in 1 placebo subject and finally injection site reaction in 1 more placebo subject.

Deaths

Over both LD studies a total of 6 patients died, 4 patients with GL (3 in the NIH study and one in the FHA101 study), 1 patient in the PL subgroup the NIH study and 1 patient in the PL group (but not subgroup) of the FHA101 study. None were considered related to treatment as underlying comorbidities were far more likely to have played a role in the patients' deaths.

In the pooled supportive obesity studies there was one death, in which the subject developed lymphocytic leukaemia one month after initiation of metreleptin treatment. The death was considered unrelated to the study drug, tough only sparse information in this case are available.

Hypersensitivity

Three patients in the GL group experienced events marked as SAEs, with one patient having neutralising antibodies at the time of event, and another withdrawing and passing away after experiencing cardiac arrest which occurred as a likely consequence of pancreatitis and treatment-unrelated septic shock. Two potential non-SAE events of severe severity were a case of dyspnoea and a case of asthma, the latter occurring in one of the three patients referenced above.

In the PL subgroup no events were considered of severe intensity and no potential hypersensitivity events in the PL subgroup were SAEs not did any lead to treatment discontinuation.

In study FHA101 2 GL patients experienced potential hypersensitivity, though neither was considered treatment related.

Among the PL patients in this study 7 reported events, with 2 of them reporting unrelated SAEs (hypotension and dyspnoea). The latter patient with dyspnoea was also ADA positive at time of event.

No events led to study discontinuation in study FHA101.

In general events were generally low in number and mild, with very few leading to discontinuation and almost no events coincided with NAb positivity.

In the supportive obesity studies the overall incidence of HS events was comparable in LD patients versus placebo treated subjects (16% vs 13%). In total 6% and 3% of metreleptin and placebo treated patients, respectively, experienced treatment related events, with urticaria being the most commonly reported in 2% of metreleptin subjects and <1% placebo subjects. Only one treatment-related event was reported as an SAE; an episode of asthma in a metreleptin receiving patient.

Hypersensitivity events leading to discontinuation, generally urticaria, affected 2% of metreleptin patients and 1% of placebo patients. Apart from urticarial and rash, which affected about 3 times the number of metreleptin patients compared to the placebo ones, all other reported HS events knew similar rates between both groups.

Hypoglycaemia

In the NIH study all reports of hypoglycaemia events in patients with GL and in the PL subgroup were mild in severity with no pattern of onset relative to treatment start and no clinical sequelae, nor discontinuations. In the GL and PL subgroup populations 12% and 10% of subjects had mild events that were considered possibly treatment-related, and 75% of them could control the event by way of dietary measures instead of diabetic medications.

In the FHA101 study there was a more outspoken imbalance between the GLA and PL subgroup patients with 22% and 43% of them having hypoglycaemic events respectively. The only events of severe intensity and that were labelled as SAEs occurred in the non-subgroup PL patients (3 cases of which 1 considered treatment-related). Nonetheless, none of the FHA101 subjects discontinued the study as all recovered from the events and continued receiving treatment.

In the supportive obesity studies hypoglycaemia was only reported in diabetic patients, and saw incidence rates of 4% versus 1% in metreleptin and placebo treated patients respectively. Among obese subjects with diabetes, the incidence of hypoglycaemia was 15% in the metreleptin 10 mg group (9 of 61 subjects), 14% in the metreleptin 20 mg group (19 of 135 subjects), and 5% in the placebo group (5 of 100 subjects). None of the reported events were considered SAEs and none led to study discontinuation.

Neoplasms

In the pooled NIH and FHA101 populations there were 17 patients whom experienced at least 1 neoplasm TEAE. Of these 70.5% continued on treatment for more than one year and moved to commercial Myalepta or expanded access programs after completion of their trail participation.

Of the 75 GL patients, 4 had events considered SEAs. Two patients discontinued treatment due to these SEAs, and 2 continued treatment after diagnosis.

In the PL subgroup two cases were considered SAEs, and in the non-subgroup PL patients there was one incident of neoplasm, also counted as SAE.

All malignancies were reported as not-related apart from one case of ALCL (described under SAEs). Apart from that case, there were also two more cases of T-cell L-lymphoma, but they were not considered related to metreleptin treatment given that severe co-morbidities (pre-existing lymphoma and/or bone marrow or haematologic abnormalities) were more likely to be the underlying cause of the neoplasm development.

In the supportive obesity trials neoplasms were exceedingly rare, and there was no difference in occurrence rate between metreleptin and placebo groups (1% vs 1%), and no T-cell lymphomas nor treatment-related events were noted.

Hepatic disorders

Consistent with the nature of the disease the majority of patients had pre-existing abnormal liver parameters and diseases.

In the NIH study 15% of GL patients and 7% of PL subgroup patients reported hepatic events, of which the majority were related to pre-existing hepatic conditions.

Five of the events in the GL group were considered SAEs and one of these led to study discontinuation and subsequent death of the patient (chronic hepatic failure and hepatic encephalopathy).

In the FHA101 study 22% of GL patients and 14% of PL subgroup patients reported mild to moderate liver function test increased and all but 1 were assessed as unrelated to study treatment.

None of these events impacted study participation. The cases in the GL patients were considered SAEs, though both patients already had elevated liver function tests at study entry.

No hepatic events were noted in the supportive obesity studies.

Autoimmune disorders

Autoimmune events occurred only in 7 NIH GL subjects, and of these only 1 did not have pre-existing underlying autoimmune disorders, though this patient had sever hepatic disease at study entry.

Reported autoimmune events were: 3 reports of autoimmune hepatitis, 2 reports each of MPGN and FSG, and 1 report of autoimmune thyroiditis. All autoimmune disorders were non-serious and assessed as unrelated to study treatment.

There were no autoimmune disorders reported for obesity studies, nor statement about their lack included into the documentation.

Serious Infections

In the NIH study about 9% of patients with GL or subgroup type PL had serious infections during metreleptin treatment, mainly sepsis/bacteraemia, pneumonia, and cellulitis.

In the GL patients of the NIH study, 11% of 66 persons developed serious infections, with only pneumonia and sepsis being reported in more than 1 person (each in 2 persons). In the PL subgroup serious infections occurred in 7% of the 31 patients, with 1 patient developing cellulitis, streptococcal infection, and pharyngitis, while the other experienced osteomyelitis and cellulitis. All serious infections were assessed as unrelated to study treatment, and none led to study discontinuation.

In the FHA101 study no serious infections were reported for neither GL nor PL subgroup patients. In non-subgroup PL patients 3 out of 25 experienced serious infections: gastroenteritis, cellulitis, infectious colitis, urinary tract infection and urosepsis. All events were considered unrelated to study treatment and there were no event-related discontinuations either.

Serious infections were reported in less than 1 percent of metreleptin or placebo subjects in the supportive obesity studies. All were SAEs by default as per protocol, though none were related to study treatment. Two metreleptin patients and one placebo patient discontinued treatment due to events of serious infection.

Pancreatitis

One of the primary metabolic abnormalities in patients with LD is severe hypertriglyceridaemia, which can result in life-threatening bouts of acute pancreatitis. In the NIH study for example about 31% of patients had prior medical history of pancreatitis.

In both NIH and FHA101 studies combined 6 patients (4 GL, 1 subgroup PL and 1 non-subgroup PL) had treatment emergent pancreatitis, and one patient developed fatal septic shock. The other 5 subjects all recovered from their episode(s) and continued treatment.

One patient however experienced non-SAE pancreatitis during treatment withdrawal (for other reasons), and this rebound pancreatitis is a known issue if treatment is stopped abruptly. Thus tapering off the metreleptin product is recommended and also adequately addressed in the SmPC.

All 5 pancreatitis events were deemed by the investigator to be severe and unrelated to metreleptin. One patient in the GL group in *Study FHA101* with a history of pancreatitis and extremely elevated triglycerides at study entry (119.9 mmol/L) experienced 3 events of pancreatitis or acute

pancreatitis during the study; all events were reported as SAEs unrelated to study treatment. Pancreatitis was not reported in any patient in the PL group.

In obesity data pool, one subject, Subject 970171-17-17022, a 39 year-old male who received metreleptin, developed pancreatitis on Study Day 90. The event, which was reported as an SAE and led to treatment withdrawal, was assessed as unrelated to study treatment by the Investigator. The event was reported as resolved 4 days after onset. No other subjects reported pancreatitis.

Time courses of serum TG levels for several of these patients were not available even in CSRs.

In the supportive obesity studies only one event occurred in a metreleptin treated patient, which led to the subject's withdrawal from the study. It was considered unrelated to treatment and safely resolved 4 days after first occurrence.

Injection site reactions

In the NIH study only 6% and 7% of GL and Pl subgroup patients respectively reported non-serious moderate intensity events, mainly injection site pain, of which none led to treatment withdrawal.

Higher number of patients (44% GL, 57% PL subgroup) reported events in the FHA101 study, but here too none were considered serious. About half of the events occurred in the first month of treatment, suggesting there is a large habituation effect, and none led to treatment withdrawal.

Injection site reactions were the most commonly reported TEAEs in the supportive obesity trials, occurring in 82% of all metreleptin patients and 54% of all placebo patients. These reactions were more common in metreleptin subjects without diabetes (85%) compared to those with diabetes (73%) with higher incidence in both groups reported at the 20 mg metreleptin dose level: 88% vs 79% in subjects with diabetes and 75% vs 67% in subjects without diabetes.

In about 77% and 37% of metreleptin and placebo treated subjects, respectively, these events were considered treatment related, and one patient in each group had an ISR that was considered an SAE.

In total 6% of metreleptin patients had an ISR that led to discontinuation, whereas this number was less than 1% in placebo patients.

Pregnancy

There have been 27 reports of metreleptin exposure during pregnancy. One report was from post marketing and the remaining 26 were from clinical studies/Investigator Initiated Studies/Expanded Access Programme. Fourteen of these pregnancies resulted in either spontaneous abortion/abortion/stillbirth or other fatal foetal outcome. It is however uncertain if the fatal foetal outcomes were due to the underlying disease of LD rather than the effect of metreleptin.

In the LD studies 4 NIH GL patients became pregnant, with two patients reporting multiple pregnancies, leading to a total of 6 incidences. Three of these patients had the pregnancies recorded as AE.

Two of the eight pregnancies resulted in live births, and both infants were seemingly healthy at the last time of check-up during the study. Both children were also breastfed during the mother's study participation, seemingly without any harmful effects. Spontaneous abortions were reported in 2 patients, one of which went on to give life birth subsequently, and 1 patients had 2 pregnancies that ended in foetal death and still birth. All foetal adverse events were considered not related to treatment, given the known association between problematic pregnancy and the LD comorbidities.

In the supportive obesity studies one patient on metreleptin became pregnant and withdrew from the study. The pregnancy was subsequently terminated, but no reason or follow-up were provided.

Immunological events

Antibodies were assessed using two different methods, chemiluminescence bridging assay and functional cell-based neutralising antibody assay, and only patients that had data from both assays available were considered for immunogenicity analysis plus two patients that had NAbs but no chemiluminescence derived data. The number of patients thus analysed is provided in **Table 47.**

Table 47. Immunogenicity data set

Disposition	NIH Study	FHA Study	Total
Total patients enrolled	107	41	148
Patients with			
Evaluable ADA data	50	24[a]	74
No ADA data available	14	17	31
Chemiluminescence bridging assay data	48	24[a]	72
Functional cell-based neutralising assay data	93	24[a]	117
Data from both assays	48	24[a]	72
Neutralising positive result without bridging assay data	2	0	2

[a] *One additional patient had chemiluminescence bridging assay and functional cell-based neutralising assay data available; however, only results obtained >4 months post-treatment were available without any baseline data. Data from this patient are not included in analyses.*

An overview of DA status in the 74 originally analysed patients, overall and per LD type is given in **Table 48.**

Table 48. Overview of Anti-Drug Antibody Status by Study

Patient Status	**NIH Study**	**FHA Study**	**Total**
Total patients enrolled	107	41	148
GL and PL Patients with Antibody Data	**50**	**24**	**74**
Anti-metreleptin antibody positive	43 (86.0)	22 (91.7)	65 (87.8)
Anti-metreleptin antibody negative	7 (14.0)	2 (8.3)	9 (12.2)
Clearing Antibodies	0	0	0
Sustaining non-neutralising antibodies	36 (72.0)	19 (79.2)	56 (75.7)
Neutralising	7 (14.0)	3 12.5)	10 (13.5)
GL Patients with Antibody Data	**38**	**3**	**41**
Anti-metreleptin antibody positive	34 (89.5)	2 (66.7)	36 (87.8)
Anti-metreleptin antibody negative	4 (10.5)	1 (33.3)	5 (12.2)
Neutralising	7 (18.4)	1 (33.3)	8 (19.5)
PL Patients with Antibody Data	**12**	**21**	**33**
Anti-metreleptin antibody positive	9 (75.0)	20 (95.2)	29 (87.9)
Anti-metreleptin antibody negative	3 (25.0)	1 (4.8)	4 (12.1)
Neutralising	0	2 (9.5)	2 (6.1)
PL Subgroup[a] with Antibody Data	**8**	**7**	**15**
Anti-metreleptin antibody positive	5 (62.5)	7 (100)	12 (80.0)
Anti-metreleptin antibody negative	3 (37.5)	0	3 (20.0)
Neutralising	0	1 (14.3)	1(6.7)

[a] *PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L, plus baseline leptin level <12.0 ng/mL (latter only for Study FHA101).*

Of the 41 GL ADA positive patients 68% had congenital form GL. In the congenital patients, 36 (88%) of 41 were positive for ADAs, and 7 (17%) developed neutralising activity.

In the NIH study ADA titres were taken for 29 GL patients and 5 patients of the PL subgroup. In the former 62% of patients had titres of 125 or less, with median time to peak around 9 months, and the 2 highest titres measured were 3000 to 50000 time more high. In the Pl subgroup 80% of subjects had titres of 125 or less, and one peak titre reached 5 times this amount. Median time to peak titre was 5.7 months.

In study FHA101, the 2 GL ADA-positive patients had peak titres of 125 and 3125, with a median time to peak of 5.3 months In the PL subgroup, 2 of the 7 ADA-positive subjects had peak titres of 625, 4 had peak titres of 3125, and 1 had a peak titre of 15,625. Median time to peak titre in this group was 7.1 months.

Of the 33 PL patients for whom ADA data was available 91% had the familial form, and 9% the acquired. Overall 88% (n=29) of PL patients had ADAs and 6% (n=2) developed neutralising ABs. In this overall group 15 patients belonged to the PL subgroup (7 from the FHA study and 8 from the NIH study), and of these 80% (n=12) had ADAs and 7% (n=1) had NAbs.

Based on FDA request a third assay was developed and used to reanalyse all banked samples, giving slightly higher evaluable numbers **Table 49**.

Table 49. Overview of Anti-Drug Antibody Status by Study and Overall for Patients with available AB data (receptor binding assay set)

Patient Status	**NIH Study**	**FHA Study**	**Total**
Total patients enrolled	107	41 (27*)	148 (134*)
GL and PL Patients with Antibody Data	**81**	**21**	**102**
Anti-metreleptin antibody positive	77 (95.1)	21 (100)	98 (96.1)
Anti-metreleptin antibody negative	4 (4.9)	0	4 (3.9)
Sustaining non-neutralising antibodies	43 (53.1)	17 (80.9)	60 (58.8)
Neutralising (>80% receptor inhibition)	34 (42)	4 (19)	38 (37.3)
GL Patients with Antibody Data	**50**	**3**	**53**
Anti-metreleptin antibody positive	48 (96)	3 (100)	51 (96.2)
Anti-metreleptin antibody negative	2 (4)	0	2 (3.8)

Neutralising	25 (50)	0	25 (47.2)
PL Patients with Antibody Data	**31**	**18**	**49**
Anti-metreleptin antibody positive	29 (93.5)	18 (100)	47 (96)
Anti-metreleptin antibody negative	2 (6.4)	0	2 (4.1)
Neutralising	9 (29)	4 (22.2)	13 (26.5)
PL Subgroup[b] with Antibody Data	**23**	**6**	**29**
Anti-metreleptin antibody positive	21 (91.3)	6 (100)	27 (93.1)
Anti-metreleptin antibody negative	2 (8.7)	0	2 (6.9)
Neutralising	6 (26.1)	0	6 (20.7)

** Although 41 patients were enrolled in study FHA101, the research protocol, which assessed antibody levels, was mainly utilised at the University of Michigan site which enrolled a total of 27 patients*
[b] PL subgroup = patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L, plus baseline leptin level <12.0 ng/mL (latter only for Study FHA101).

For the 35 patients with GL, 35 had the congenital form of the disease and 18 had the acquired form. In this group of patients with GL, while for the 49 PL patients with available 43 had the familial form of the disease and 6 patients had the acquired form.

In the PL subgroup, 25 of 29 subjects had the familial form of the disease and 4 patients had the acquired form.

Safety by ADA response

An overview of the TEAEs by ADA status in the analysed GL and PL patients is provided in **Table 50.**

Table 50. Overall Summary of TEAEs by Anti-Leptin Binding Antibody Status (NIH & FHA101, Antibody AS)

Patients with at least one:	GL		PL subgroup[a]	
	POSITIVE (N=36) N (%)	NEGATIVE (N=5) N (%)	POSITIVE (N=12) N (%)	NEGATIVE (N=3) N (%)
TEAE	32 88.9)	4 (80.0)	11 (91.7)	3 (100.0)
Drug-Related TEAE	21 (58.3)	1 (20.0)	6 (50.0)	2 (66.7)
Severe TEAE	17 (47.2)	3 (60.0)	3 (25.0)	2 (66.7)
Drug-Related Severe TEAE	7 (19.4)	0	0	0
Treatment-emergent SAE	15 (41.7)	2 (40.0)	2 (16.7)	1 (33.3)
Drug-Related Treatment-Emergent SAE	3 (8.3)	0	0	0
TEAE Leading to Study Drug Discontinuation	2 (5.6)	1 (20.0)	1 (8.3)	0
On-Study Deaths	1 (2.8)	1 (20.0)	1 (8.3)	0

Abbreviations: HbA1c = haemoglobin A1c; PL = partial lipodystrophy; 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, plus baseline leptin level <12.0 ng/mL (latter only for Study FHA101).*

Based on review of the data, 9 patients with GL and 4 patients in the PL subgroup had potential hypersensitivity events that occurred while the patient was positive for ADAs.

For those PL patients who weren't included in the PL subgroup, 6 reported hypersensitivity events concurrent with ADAs, but the only events of severe intensity were dyspnoea/flushing/asthma in 1 GL patient, urticaria in another GL patient; and dyspnoea in 1 PL subject who was not part of the PL subgroup.

Two GL patients had concurrent autoimmune disorders during their ADA positive status. One presented with membranoproliferative glomerulonephritis, and the other had neutralising antibodies at the same time as focal segmental glomerulosclerosis was diagnosed.

Three patients with GL and 1 patient in the PL subgroup were positive for ADAs when they were reported with severe infection. This included 3 GL patients of which 2 had sepsis (though the significant comorbidities may have been rather to blame) and 1 had appendicitis. The PL subgroup

patients had a serious infection with streptococcal pharyngitis. In the non-subgroup PL patients there were 4 ADA-positive patients with serious infections.

In the results obtained through the new receptor based analysis it does not appear that there are any significant differences between neutralising positive and neutralising negative groups for the PL/PL subgroup patients (data not shown). However, in the GL patients there seems to be a clear trend towards more treatment emergent incidences in the Nac positive population (96% Vs 80.8).

Analysis of Infections in Lipodystrophy Patients (receptor binding assay set)

In order to better characterise any potential association of NAbs and infection the Applicant ran a number of reviews on the data. One such review aimed to determine the full nature and extent of all temporally associated infections among the 38 NAb positive patients, and this revealed a total of 34 temporally related adverse events (AEs) of infection in 16 patients. Of these only 13 were severe, 7 of which occurred in the same patient, and 12 of the severe cases were also labelled as an SAE.

In the GL group 5 patients were stricken by serious or severe events associated with NAc, including 1 episode of serious and severe appendicitis, 2 episodes of serious and severe pneumonia, a single episode of serious and severe sepsis and non-serious severe gingivitis in 1 patient, and 6 episodes of serious and severe sepsis or bacteraemia and 1 episode of non-serious severe ear infection in 1 patient.

In the PL subjects One serious and severe infection of appendicitis was temporally associated with NAc in an non-subgroup subject, whereas no NAc associated events occurred in the PL subgroup patients. None of these events were considered related to treatment by investigators and all events resolved without sequelae.

Analysis of neoplasms in Lipodystrophy Patients (receptor binding assay set)

Neoplasms were reported in 14 of the 102 patients with antibody data for analysis, including 8 (15%) of 53 patients with GL and 6 (12%) of 49 patients with PL, including 5 (17%) of 29 patients in the PL subgroup. Of these patients seven were ADA positive/neutralising positive at some time during the study (not necessarily at the time of the reported event).

A total of 5 events in 4 patients who were ADA positive/neutralising positive and 4 events in 4 patients who were neutralising negative were assessed as benign. Contrarily, 7 patients, including 6 with GL and 1 with PL who was not in the PL subgroup reported malignant neoplasms during treatment with metreleptin, including intraductal proliferative breast lesion, peripheral T-cell lymphoma, basal cell carcinoma, ovarian neoplasm, papillary thyroid cancer, anaplastic large-cell lymphoma, and squamous cell carcinoma of the eyelid.

Of the 7 patients with malignant carcinomas only 3 patients, all GL, developed NAc. Of these 3 latter subjects 2 were NAb negative at the time of the reported malignancy, whereas the remaining ALCL, had NAc at the time of the reported malignancy. This latter patient had treatment suspended for 6 weeks but had to return to treatment after 6 weeks due to recurrence of metabolic abnormalities associated with her underlying LD. Her malignancy was cured, and after the restart of treatment she remained on metreleptin, completed the study and was started on commercial product.

Clinical impact analysis following reanalysis using new receptor-based assay

A medical review was conducted to assess both the potential and actual clinical impact for the 19 patients with attenuated/worsening efficacy and NAc, using a scale of 1 to 5 (1 being minimal impact and 5 being severe impact). This analysis took into consideration all AEs temporally associated with NAc, with special consideration and higher scoring for AEs that were serious, severe, related or OSAEs.

Of the 19 patients, 6 had PL and 2 of those were part of the PL subgroup. The mean actual impact score for GL patients was 2.4, and for PL patients was 1.5. The 2 PL subgroup patients had favourable clinical courses, with actual impact scores of 1 and 2. Mean actual impact scores did not differ between patients with transiently and persistently affected efficacy parameters (2.2 vs 2.0 respectively).

Of note is the fact that one of the most significant comorbidities associated with poor metabolic control in lipodystrophic patients, i.e., acute pancreatitis, was not seen temporally associated with NAc in any of these 19 patients with attenuated or worsened efficacy, despite extremely high levels of triglycerides.

The highest actual clinical impact scores of 5 were allocated to 3 GL patients who experienced multiple SAEs temporally associated with NAc, including serious and severe sepsis. Two GL patients with an actual impact score of 3 experienced unrelated severe SAEs of pneumonia. Two patients, one GL patient and one PL patient not in the PL subgroup developed serious and severe AEs of appendicitis with an impact score of 2.

One specific concern in PL patients with residual leptin levels who develop a neutralising ADA response and who also report a loss of clinical efficacy is that the NAb will cause clearing of metreleptin and endogenous leptin from the body leaving the patient more compromised than at baseline.

Overall, 13 PL patients developed NAc across both main studies, and of these 6 patients (46.2%) had apparent attenuation or worsening of efficacy at the time they developed NAc, including 2 (33%) of 6 patients in the PL subgroup, compared to 17 patients with efficacy loss that did not develop a NAc. Other than 2 serious events (including one of appendicitis and one of dyspnoea, both severe and unrelated to metreleptin treatment), AEs were generally mild to moderate in severity and not related, or not temporally associated with the development of NAc.

Supportive obesity studies

In the 5 supportive PhII obesity studies a total of 379 patients received metreleptin, and of those 324 (85%) had at least one confirmed incidence of ADA positive status (as opposed to 5 (2%) of the 247 placebo patients).

A higher incidence of TEAEs was reported in subjects who had at least 1 positive ADA result (95%) compared to subjects who were ADA negative (86%) or who received placebo (86%). This difference was mainly due to the difference of injection site reaction rates: 87% of subjects with at least 1 post baseline ADA positive result experienced injection site reaction compared with 68% of subjects who ADA negative and with 54% subjects who received placebo. The only other common TEAE reported at a higher incidence in ADA positive subjects was nasopharyngitis (14%).

Incidence of SAEs was 2% versus <1% and 4% respectively (ADA+, ADA-, Placebo, respectively). Injection site reaction was the only potentially immune-related TEAE experienced by 5% of subjects or more in any treatment group. Other potentially immune-related TEAEs reported in >1% of metreleptin subjects with positive ADAs (with corresponding incidence in subjects negative for ADAs) were cough (3% vs 4%), rash (3% vs 2%), peripheral oedema (2% each), urticaria (2% vs 1%), and hypersensitivity (1% vs 0%).

Laboratory findings

Review of clinical laboratory data across patients with LD in the NIH study and Study FHA101, including haematology, clinical chemistry, and urinalysis (Study NIH 991265/2001769 only) did not reveal any safety signals for metreleptin treatment.

In both studies small mean changes from baseline were noted at Months 12 and 24 for haematology parameters, including haemoglobin, WBC and platelet count with consistent mean values noted over time in both the GL group and the PL subgroup, with the former showing relatively larger changes.

Electrolytes, including sodium, potassium, and chloride, as well as renal function tests showed only small mean changes from baseline to Months 12 and 24 with consistent mean values noted over time for both the GL group and PL subgroup in the NIH study.

No clinically meaningful changes over time on metreleptin treatment in other parameters.

Review of clinical laboratory data across subjects in the supportive obesity studies pool, including haematology, chemistry, lipid parameters, thyroid function, and urinalysis did not reveal any safety signals for metreleptin treatment.

Vital Signs

LD study subjects experienced only small mean changes from baseline to Months 12 and 24 in systolic/diastolic blood pressure and heart rate and generally showed improvement over time on treatment in both patients with GL and in the PL subgroup.

Both studies also generally noted mean decreases in weight during treatment with metreleptin as shown in **Table 51**.

Table 51: Mean weight change in subject subgroups (pooled NIH and FHA101 studies)

Patient group / Time point	6 Months (mean weight change in kg)	12 Months (mean weight change in kg)	24 Months (mean weight change in kg)
NIH study, GL group	-2.8	-2.7	-1.4
NIH study, PL subgroup	-0.6	-0.7	-0.7
FHA101 study, GL group	-2.5	-2.9	+1.2
FHA101 study, PL subgroup	-1.0	-0.5	-1.7

Overall 44% of paediatric patients in NIH study were reported to have had growth complete or near complete prior to entry. Among the remaining 20 paediatric patients, 10 were reported to have normal growth, 2 had growth acceleration and 8 had growth deceleration. The 2 patients in the PL subgroup had growth complete or near complete at study entry and among the two other non-subgroup PL patients one had growth deceleration reported during metreleptin treatment.

Thirty-three NIH patients younger than 18 years of age had pubertal status assessed at baseline. Twenty-six of these patients had puberty complete, near complete, or likely complete 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.

Of the 36 NIH patients for whom Tanner Stage scoring was available at baseline and on treatment, 12 had completed puberty prior to metreleptin treatment and 3 patients were prepubertal throughout the study (normal for their age). Among the remaining 21 patients, 14 underwent normal pubertal development, 2 had precocious puberty reported prior to the start of treatment with normal or slow progression on treatment, 3 patients had possible slow progression (including 1 with

delayed development at the start and 1 with delayed development during treatment interruption), 1 had slight precocious development during treatment, and 1 patient who was extremely ill had lack of pubertal progression.

Sixteen NIH patients were assessed for bone age at study baseline and had additionally at least 1 post-baseline assessment; approximately half of the patients had bone age >2 years higher than their birth age at study entry; one patient had younger bone age. All 16 patients were reported as growing on metreleptin treatment.

Review of vital signs data in the supportive obesity studies did not reveal any safety signals for metreleptin treatment.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies were submitted, but it is acknowledged that metreleptin has the potential to alter the formation of cytochrome P450 (CYP450) enzymes.

Discontinuation due to adverse events

In the NIH and FHA101 studies overall withdrawal rates due to TEAEAs were 6% and 10% of patients respectively.

In the NIH study all TEAEs leading to withdrawal were considered not treatment-related and each type of TEAE only occurred in 1 patient each. Four of the six incidents had a fatal outcome.

One patient with underlying liver disease withdrew due to increased blood triglycerides and inadequate control of diabetes mellitus. The patient was ADA negative at baseline, but tested positive after 6 months of treatment. At month 24 low level neutralising ab activity was detected and HbA1c and triglyceride levels were increasing from the Month 20 assessment levels. At Month 42 levels had continued to rise and the patient was tapered off treatment.

In the FHA101 study equal rates of GL and non-subgroup PL patients withdrew due to TEAEAs, though no PL subgroup discontinued treatment. All TEAEs leading to withdrawal occurred in at most 1 patient each.

One event was considered related to treatment. After approximately 8 months on treatment, the patient experienced muscle spasms, and treatment with metreleptin was held. The patient was discontinued from the study 6 months due to the AE of muscle spasms.

Post marketing experience

As of 24/07/2016, 138 patients (116 in the US and 22 in Japan) had been receiving commercial Myalepta or equivalent.

Deaths

Two cases of fatal outcome have been received, one of which was likely a complication of the patients underlying prior advanced liver cirrhosis, and who discontinued treatment with metreleptin somewhere within 4 to 6 weeks due to complications of the former. The other case died of unknown causes about one year and a month after metreleptin treatment initiation, but had suffered a possible stroke 4 months earlier.

Given the timings and the underlying comorbidities it seems unlikely that metreleptin was a direct causal parameter in these patients' deaths.

(S)AEs

The most commonly reported attributable ICSRs (>5 reports) were weight decreased (14 cases, none serious), nausea (10 cases, 2 serious), blood glucose increased (8 cases, 3 serious), hyperphagia (7 cases, none serious), headache (7 cases, none serious), and blood triglycerides increased (6 cases, 2 serious).

Identified safety concern: Hypersensitivity

In total 24 cases were received, and amongst these anaphylactic reaction was reported twice in 1 serious case with evidence of positive dechallenge and rechallenge. There were also 4 non-serious cases of urticaria of which only 1 was unresolved at reporting time, and finally there was 1 resolved non-serious case of generalised rash.

Identified safety concern: Acute Pancreatitis

In total 16 cases were reported upon, including 2 cases of pancreatitis (1 resolved and 1 unknown), 1 of acute pancreatitis (resolved) and 1 case of relapsing pancreatitis (unknown). All cases were considered serious. No identification on the precise type was provided for the other 12 received reports.

One case of pancreatitis was associated with treatment interruption/non-compliance, and one other case of pancreatitis as well as a case of acute pancreatitis led to patient hospitalisation.

Identified safety concern: Hypoglycaemia with Concomitant Use with Insulin and Insulin Secretagogues

A total of 4 cases were received, seeing concomitant use of insulin in and concomitant use of metformin in 3 of them. In 2 cases the events were resolved, in 1 it was not resolved and in 1 case the status was unknown.

In all of the cases retrieved, the analysis was non-conclusive as other confounding factors (medical history of diabetes and/or previous episodes of hypoglycaemia) were present.

Identified safety concern: Lymphoma

No cases received.

Identified safety concern: Loss of Efficacy Due to Neutralising Activity

There were 4 reports of NAb positivity received, including a case where therapeutic response decreased. In one of the cases, a positive de-challenge and re-challenge of anaphylaxis was reported and Metreleptin was permanently discontinued but there were no details regarding the loss of efficacy.

The two other cases of confirmed NAb positivity involved two severely obese children of unknown sex and age receiving metreleptin for congenital leptin deficiency.

Identified safety concern: Use in Elderly

No new relevant information was identified.

Identified safety concern: Use in Pregnancy and Lactation

Only 1 pregnancy report was received, detailing an abortion that involved a 33 year old female who was receiving fertility treatment. Information pertaining to last menstrual period and trimester of pregnancy outcome was not provided. It is also not clear whether this abortion was spontaneous or provoked.

Use in renal impairment

There have been a cumulative total of 3 reports, for a total of 54 AEs (of which 15 were serious).

The most frequently reported AEs were nausea, blood glucose decreased, decreased appetite, fatigue and therapy cessation; all of these were non-serious.

Reported SAEs included abdominal pain, abdominal pain upper, acute kidney injury, blood glucose increased, diabetic ketoacidosis, hyperglycaemia, hyperkalaemia, hypertriglyceridaemia, hypoglycaemia, metabolic acidosis, metabolic encephalopathy, pancreatitis acute, pneumonia, staphylococcal infection and vomiting; all events were reported one time each.

2.6.1. Discussion on clinical safety

The safety of metreleptin was assessed in 2 LD studies that recruited all 4 forms of the syndrome (CGL, AGL, FPL and APL), supported by results in 5 PhII studies that had aimed to investigate the effectiveness of treating obesity with metreleptin.

Across the 2 LD studies, a total of 148 patients were enrolled, including 75 patients with GL and 73 patients with PL, of whom 38 were included in a subgroup of PL patients who have similar metabolic abnormalities related to their underlying disease as patients with GL and were thought to have similar benefit of metreleptin as the latter. The vast majority of these patients were treated for at least 1 year, and about half for more than three years even, given a total patient exposure of more than 500 patient years.

The majority of participating GL subjects were females, younger than 18 years of age, and about 63% of GL patients had CGL. PL patients were generally older and almost exclusively female. Very few patients older than 65 or younger than 6 years were included in these studies. Whilst it is acknowledged that elderly LD patients are relatively rare, as elderly patients in general have a markedly different safety profile form young people, use in the elderly is included in the RMP as missing information and further information in this population will be collected through the planned registry with lipodystrophy patients.

The majority of reported events that were considered related to metreleptin treatment could be expected given the nature of the investigative product. Some of the more serious reported events such as cardiac arrest or liver failure, and a number of deaths, are more likely explained by the underlying syndrome comorbidities.

A number of specific AEs were considered of special interest.

Given that the product is a protein-analogue, hypersensitivity reactions can be expected following metreleptin administration. There have been a number of reports of generalised hypersensitivity (e.g. anaphylaxis, urticaria or generalised rash) in patients using Myalepta. The product information includes a number of warnings for this risk, including a contraindication for those with hypersensitivity to the active substance (or to any of the excipients), and that administration should be permanently discontinued immediately and appropriate therapy initiated if an anaphylactic reaction or other serious allergic reaction occurs.

As metreleptin improves insulin resistance, there is a potential for hypoglycaemia to occur if used in concurrence with antidiabetic medications is possible and adjustment of antidiabetic medications may be required. As hypoglycaemia occurred in several patients, this has been included in the RMP as an important identified risk. A warning has been included in the product information risk of hypoglycaemia in patients treated with Myalepta who are on anti-diabetic medicinal products, in particular insulin or insulin secretagogues (e.g. sulphonylureas). Large dose reductions of 50% or more of baseline insulin requirements may be needed in the first 2 weeks of treatment. Once insulin requirements have stabilised, dose adjustments of other anti-diabetics may also be needed in some patients to minimise the risk of hypoglycaemia. Furthermore, patients should be closely monitored for blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogues and combination treatment. Patients and carers should also be advised to be aware of the signs and symptoms of hypoglycaemia. In case of hypoglycaemic events of a non-severe nature, food intake management may be considered as an alternative to dose-adjustment of anti-diabetics according to the treating physician's opinion, in line with the management of these patients in the clinical trials.

Another event of particular interest was, acute pancreatitis as a consequence of hypertriglyceridaemia which is relatively common in LD patients. In the conducted studies there have been a number of treatment-related bouts of pancreatitis, including one fatality. The reported events may have been linked to abrupt interruption and/or non-compliance with metreleptin dosing. The mechanism for this could be a rapid return of hypertriglyceridaemia. The risk of pancreatitis associated with discontinuation of treatment has also been included in the RMP as an important identified risk and the product information advised that patients who require discontinuation of metreleptin should be tapered off treatment over a period of two weeks and should not stop metreleptin abruptly.

T-cell lymphoma occurred in 3 AGL patients, of which one died. Given the possible autoimmune potential of metreleptin, T-cell lymphoma is an event of interest. However, AGL as well as type 2 diabetes, are risk factors for lymphoma. Reassuring in this regard is the fact that there have been no additional reports of T-cell lymphomas in the post-marketing setting as of July 2016. Nonetheless lymphomas are considered an important potential risk in the RMP and caution is advised for use of the product in patients with significant haematological abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy).

Immunogenicity is considered a major point of interest given the nature of the product. Furthermore, endogenous leptin and metreleptin differ by only one amino acid which could lead to the additional complication that ADAs, and more worryingly neutralising antibodies, to metreleptin cross-react with endogenous leptin. Following the initial evaluation the applicant provided data available from an FDA-mandated immunogenic re-evaluation of available samples using a newly developed receptor-based assay. Though the more sensitive assay identified more ADA and Nab positive subjects, the clinical correlations were broadly in line with the findings in the less sensitive prior testing.

Across the 2 LD studies, over eighty percent of patients for whom a ADA data was available developed an immunogenic response to metreleptin. For the majority of patients, the ADA response was a sustaining non-neutralising response of little or no clinical consequence. Given that the clinical course of patients with LD is very complicated, and that in any given patient, disease severity and its natural course is poorly understood, characterisation of the actual impact of ADAs on these patients is challenging to evaluate. In general, review of immune-related and serious or severe infections in patients who were ADA positive did not raise specific safety concerns for either patients with GL or the PL subgroup.

Only 10 patients with ADA data available developed NAb according to the original analysis, but this number increased to 38 when analysed with the receptor binding assay. Review of immune-related AEs and serious or severe infections in this group of patients with neutralising antibody activity did generally not indicate any clear pattern or significant safety concerns. However, based on the receptor assay re-evaluation at least a temporal coincidence of severe/serious infections and Nab formation was noted, though given the limited size of the data set it is not possible to draw definitive conclusions on a causal association. Importantly, review of the clinical courses for patients with PL, who have residual leptin activity where there is concern for the development of clearing ADAs that could result in a loss of both metreleptin and endogenous leptin, showed no obvious effect of neutralising activity; there were no immune-related AEs in these patients at the time of neutralising activity.

Metreleptin therapy of PL patients with endogenous leptin levels of similar magnitude of normal values or even falling into the normal leptin level region raises a further concern. Binding of neutralising ADA to this remaining endogenous leptin might result in a complete loss of leptin activity and a deterioration of the PL after cessation of metreleptin treatment. This raises a serious safety concern for metreleptin administration in PL.

However, currently there is no sufficient confirmative data on this potential issue available and this concern thus remains theoretical at present.

Overall, the data on neutralising response is fairly limited and not robust enough to fully preclude issues occurring due to NAb development. Nevertheless, serious and severe infections secondary to Nabs and loss of efficacy potentially due to Nabs have been included in the RMP as important potential risks.

As has been discussed in the clinical efficacy section of this report, the applicant will further investigate the formation of antidrug antibodies via a detailed immunogenicity strategy. This will include validation of new assays that will allow to determine the effect of NAb on endogenous leptin levels which currently is not possible. The new assays will be used on historical samples but also new samples collected from patients in the registry and other planned studies with metreleptin. In addition, the results of a 36- month, multicentre, open-label Phase 4 study to evaluate the immunogenicity of daily SC metreleptin treatment in patients with GL will be submitted.

Abortions, stillbirths and preterm deliveries have been reported in association with metreleptin use and thus effective contraception during treatment is advised. As a precautionary measure, it is preferable to avoid the use of metreleptin during pregnancy.

Additionally, leptin plays a role in the hormonal cycle and is known to influence the release of LH hormone. Even though restoration of hormone balance may be seen as a possible positive side effect, it also raises the danger that uninformed patients whom thought themselves infertile could suddenly be faced with unexpected and potentially unwanted pregnancies. A warning therefore regarding unexpected pregnancy has been included in the product information. This concern will also be addressed in the planned Patient Registry, which will allow to collect data on the restored fertility possibly leading to an unanticipated pregnancy in addition to data on pregnancy.

It is unknown whether metreleptin or its metabolites are excreted in human milk, though it is known that endogenous leptin is present in human milk. A risk to newborns / infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from metreleptin therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

No interaction studies have been performed in humans. This was considered acceptable. However, as leptin is a cytokine it has the potential to alter the formation of cytochrome P450 (CYP450) enzymes. Since it cannot be excluded that metreleptin may reduce exposure to substrates of CYP3A

through enzyme induction, the efficacy of hormonal contraceptives may be reduced if co-administered with metreleptin. Therefore, an additional non-hormonal contraceptive method should be considered during treatment. The effect of metreleptin on CYP450 enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of metreleptin, in patients being treated with these types of agents, therapeutic monitoring of effect (e.g., warfarin), or drug concentrations (e.g. cyclosporin or theophylline) should be performed and the individual dose of the agent adjusted as needed. When starting therapy with Myalepta there is a risk of hypoglycaemia in patients who are on anti-diabetic medicinal products, in particular insulin or insulin secretagogues.

Based on the available presentation and the small volumes of the product to be administered the CHMP considered that there is a high risk of medication errors which are therefore included as an important identified risk in the RMP. In order to address this, the product information includes detailed instructions on the stating dose and dose adjustment calculations based on the patient's gender and weight. Moreover details of the required syringe, needle gauge and length is also included as well as a conversion table of the dose of Myalepta, the amount of solution required and the 'Unit' measurement volume in 0.3 mL U100 insulin syringe to inject. In addition, the patient will also receive separately the solvent for reconstitution (i.e. water for injection), the syringes/needles for reconstitution, the syringes/needles for administration, the cleansing alcohol swabs, and a sharps disposal container.

Finally educational material will be provided to healthcare professionals, patients and care-givers to ensure the continued correct and compliant Myalepta reconstitution and dose adherence, and provide training on how to reconstitute metreleptin, measure the correct dose and self-administer metreleptin to reduce medication errors. Given the wide range of identified and potential risks associated with metreleptin use the educational material will also will highlight this risks and to help ensure that the HCPs using metreleptin are made aware of the risks and will be able to monitor and adjust the treatment accordingly.

A number of additional actions for leptin have been stipulated based on clinical and non-clinical observations. For instance, leptin may increase levels of LH and there is a theoretical concern that leptin replacement in young leptin-deficient children might initiate precocious puberty as a consequence of these increased LH levels.

Leptin deficient mice, have both decreased brain weight and cortical volume that can be corrected with early leptin administration. Similarly, in three congenitally leptin deficient human adults, leptin treatment has been shown to increase grey matter volume in cerebellum, inferior parietal, and anterior cingulate cortices. Furthermore, in these same patients, small reductions in grey matter volume were detected in these same areas when leptin treatment was discontinued. Furthermore, in these same patients, small reductions in grey matter volume were detected in these same areas when leptin treatment was discontinued. In healthy adults, plasma leptin levels have been associated with total brain volume, independent of body size (Farr, 2015 Metabolism).

The leptin receptor can be found in adult primary osteoblasts and chondrocytes, suggesting that the effects of leptin on bone growth and metabolism may be direct. Although leptin may act peripherally on bone, central leptin administration in mice lacking leptin has been found to restore bone mass to control levels, suggesting that leptin may indirectly impact bone mass

Based on these observations, "Effect of increased levels of LH above normal ranges in the paediatric population", and effect of metreleptin on brain and bone metabolism have been included in the RMP as missing information and information on these issues will be collected through the disease registry.

Additional safety data needed in the context of a MA under exceptional circumstances

Taking into account the limitations of the available data arising from the rarity and heterogeneity of the disease, the CHMP was of the view that the data set on the clinical safety of Myalepta under normal conditions of use could not be considered comprehensive. This was due to the size of the clinical trials and the lack of a control treatment group which given the multiple co-morbidities and co-medications of the studied population would be required to allow determination of causality between the reported events and metreleptin use.

The CHMP was therefore of the view that a marketing authorisation under exceptional circumstances should be granted subject to specific obligations. These include the implementation of the registry to evaluate the long term safety profile of Myalepta especially with regards to the important identified and potential risks associated with metreleptin use and the provision of an integrated immunogenicity report, using validated assays for the detection of anti-drug antibodies and neutralising antibodies and analysing all available sample from patients with generalised and partial lipodystrophy from past and future studies conducted with Myalepta.

2.6.2. Conclusions on the clinical safety

Despite the limited size of the safety database, due to the rarity of generalised and partial lipodystrophy, the overall safety profile of metreleptin is considered acceptable. The main safety concerns identified are of acute pancreatitis associated with discontinuation of metreleptin, hypoglycaemia with concomitant use with insulin and other antidiabetics, immunogenicity and the potential for medication errors and which are addressed adequately through appropriate and routine and additional risk minimisation measures.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

• The patient registry to evaluate the long-term safety profile Myalepta, especially in relation to acute pancreatitis associated with discontinuation of metreleptin, hypoglycaemia with concomitant use with insulin and other antidiabetics, lymphoma, immunogenicity and medication errors

• An integrated immunogenicity report using validated assays for the detection of anti-drug antibodies from all available data in order to further investigate the clinical significance of the immunogenicity of metreleptin (ADAs and NAbs)

2.7. Risk Management Plan

Safety concerns

SUMMARY OF SAFETY CONCERNS	
Important identified risks:	Hypersensitivity (Anaphylaxis, Urticaria and Generalised Rash) Acute Pancreatitis Associated with Discontinuation of Metreleptin Hypoglycaemia with Concomitant Use with Insulin and Other Antidiabetics Medication Errors
Important potential risks:	Lymphoma Serious and Severe Infections Secondary to NAbs Unplanned Pregnancy Loss of Efficacy, Potentially Due to NAbs
Missing information:	Use in Pregnancy and Lactation Use in the Elderly Effect of Metreleptin on Brain Development Effect of Metreleptin on Bone Metabolism Effect of increased levels of LH above normal ranges in the paediatric population

Pharmacovigilance plan

STUDY (STUDY SHORT NAME, AND TITLE) STATUS (PLANNED/ON-GOING)	SUMMARY OF OBJECTIVES	SAFETY CONCERNS ADDRESSED	STATUS (PLANNED, STARTED)	DATE FOR SUBMISSION OF INTERIM OR FINAL REPORTS (PLANNED OR ACTUAL)
Patient registry (2)	Characterise the treatment of patients with metreleptin and to evaluate the long-term safety and effectiveness under conditions of usual clinical practice.	Hypersensitivity, Acute Pancreatitis Associated with Discontinuation of Metreleptin, Hypoglycaemia with concomitant use of insulin and other antidiabetics, Medication errors, Lymphoma, Serious and severe infections secondary to NAbs, Unplanned pregnancy, Loss	Planned	Protocol submission: Within 6 months of EC approval. Annual reports will be provided with the annual re-assessments for the duration of the lifecycle of the product

STUDY (STUDY SHORT NAME, AND TITLE) STATUS (PLANNED/ON-GOING)	SUMMARY OF OBJECTIVES	SAFETY CONCERNS ADDRESSED	STATUS (PLANNED, STARTED)	DATE FOR SUBMISSION OF INTERIM OR FINAL REPORTS (PLANNED OR ACTUAL)
		of efficacy potentially due to NAbs, Use in Pregnancy and Lactation, Use in Elderly, Effect of Metreleptin on Brain Development, Effect of Metreleptin on Bone Metabolism, Use in Children under 2 Years of Age (off label), Effect of increased levels of LH above normal ranges in the paediatric population		
Integrated immunogenicity report	To further characterise the effect of metreleptin treatment on ADA formation and on endogenous leptin levels, using validated immunogenicity assays and mass spectrometry. The report will include all available historical samples from previous studies (NIH991265/20010769, FHA 101, and obesity studies) with patients with GL/PL and samples obtained from patients that will be included in efficacy study in PL patients, PIP study and registry, using a reliable and validated method for the detection of antibodies + their validation reports.	Serious and Severe Infections Secondary to NAbs Loss of Efficacy, Potentially Due to NAbs		Protocol submission: Within 6 months of EC approval. Reports will be provided to the EMA at 2 years (2020), 4 years (2022) with final report at 6 years (2024) following approval. Complete data and the final report for the Study AEGR-734-401 will be appended to the 2020 integrated immunogenicity report.
AEGR-734-401: A 36-Month,	Primary objective: Evaluate the	Serious and severe infections	Planned	December 2022

STUDY (STUDY SHORT NAME, AND TITLE) STATUS (PLANNED/ON-GOING)	SUMMARY OF OBJECTIVES	SAFETY CONCERNS ADDRESSED	STATUS (PLANNED, STARTED)	DATE FOR SUBMISSION OF INTERIM OR FINAL REPORTS (PLANNED OR ACTUAL)
Multicentre, Open Label Phase 4 Study to Evaluate the Immunogenicity of Daily SC Metreleptin Treatment in Patients with Generalised Lipodystrophy (3)	immunogenicity associated with daily SC metreleptin treatment in patients with congenital or acquired GL. Secondary objective: Assess 2 methods of measuring *in vitro* NAc to metreleptin. Safety objectives: Evaluate the safety and tolerability in relation to the development of or absence of anti-metreleptin or anti-huL antibodies, and/or *in vitro* NAc to metreleptin in patients with congenital or acquired GL. Measure *in vitro* NAc in all patients with suspected loss of response (worsening of metabolic control) or endogenous leptin action (severe infections or sepsis) at time of AE report. Exploratory objective: Evaluate the efficacy achieved with daily SC metreleptin treatment in patients with congenital or acquired GL.	secondary to NAbs Loss of efficacy, potentially due NAbs		

Risk minimisation measures

SAFETY CONCERN	ROUTINE RISK MINIMISATION MEASURES	ADDITIONAL RISK MINIMISATION MEASURES
Hypersensitivity (Anaphylaxis, Urticaria and Generalised Rash)	4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	Educational materials for HCPs and patients/caregivers
Acute Pancreatitis Associated with Discontinuation of Metreleptin	4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	Educational materials for HCPs and patients/caregivers.
Hypoglycaemia with Concomitant Use with Insulin and Other Antidiabetics	4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	Educational materials for HCPs and patients/caregivers.
Medication Errors	4.2 Posology and Method of Administration 4.9 Overdose 6.3 Shelf life 6.4 Special precautions for storage 6.6 Special precautions for disposal and other handling PIL	Medication errors can be minimised by a comprehensive approach that includes the following elements: **Packaging Design** The package is designed as a compact carton containing 30 vials which is equivalent to a month's supply.

SAFETY CONCERN	ROUTINE RISK MINIMISATION MEASURES	ADDITIONAL RISK MINIMISATION MEASURES
	Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	**Educational and Training Activities** The sponsor will initiate a programme of educational activities for prescribers, patients (and their care-givers) and pharmacists dispensing the product containing key elements as follows: • Reminders on key prescribing information • Responsibility of the prescribing physician to provide appropriate training to the patient/care-giver • Requirement to perform regular follow-ups with the patient/care-giver to ensure continued correct and compliant Myalepta reconstitution and treatment • Guidance on the appropriate syringe size ancillary administration set to prescribe and dispense according to the dosage of Myalepta • Copies of the SmPC and PIL/IFU HCPs, patients, and care-givers will also be provided access to further materials, including training videos in multiple languages that will demonstrate each step to in preparing and administering Myalepta.
Lymphoma	4.4 Special warnings and precautions for use 4.8 Undesirable effects PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	Educational materials for HCPs and patients/caregivers
Serious and Severe Infections Secondary to NAbs	4.4 Special warnings and precautions for use 4.8 Undesirable effects PIL	Educational materials for HCPs and patients/caregivers.

SAFETY CONCERN	ROUTINE RISK MINIMISATION MEASURES	ADDITIONAL RISK MINIMISATION MEASURES
	Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	
Unplanned Pregnancy	4.4 Special warnings and precautions for use 4.6 Fertility, pregnancy and lactation PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	Educational materials for HCPs and patients/caregivers.
Loss of Efficacy, Potentially Due to NAbs	Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	Educational materials for HCPs and patients/caregivers.
Use in Pregnancy and Lactation	4.6 Fertility, Pregnancy and Lactation 5.3 Preclinical Safety Data PIL Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	None
Use in the Elderly	4.2 Posology and Method of Administration Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	None
Effect of Metreleptin on Brain Development	Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	None
Effect of Metreleptin on Bone Metabolism	Prescription only medicine Use restricted to physicians experienced in the management of metabolic disorders	None
Effect of Increased Levels of LH Above Normal Ranges in the Paediatric Population	Prescription only medicine Use restricted to physicians experienced in the	None

SAFETY CONCERN	ROUTINE RISK MINIMISATION MEASURES	ADDITIONAL RISK MINIMISATION MEASURES
	management of metabolic disorders	

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request international harmonisation of the PSUR cycle by using the forthcoming Data Lock Point 24.01.2019, based on the IBD of 25.03.2013.

New Active Substance

The applicant declared that metreleptin has not been previously authorised in a medicinal product in the European Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Myalepta (metreleptin) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Lipodystrophy syndromes are clinically heterogeneous inherited or acquired ultra-rare disorders characterised by selective but variable loss of adipose tissue. The loss of adipose tissue in patients with LD can range from partial to more generalised, and some patients have concomitant accumulation of excess adipose tissue centrally. Because of the loss of adipose tissue, levels of the adipocyte-secreted hormone leptin are very low. Leptin is a naturally occurring, adipocyte-derived hormone and an important regulator of energy homoeostasis, fat and glucose metabolism, reproductive capacity, and other diverse physiological functions. Circulating levels of leptin closely correlate with the amount of fat mass present. The leptin deficiency observed in patients with LD results in a significant reduction in the ability to regulate hunger and energy, as well as glucose and fat metabolism.

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

3.1.2. Available therapies and unmet medical need

For patients with LD and associated diabetes and/or hypertriglyceridaemia, current available therapies include diet modification (low calorie, low fat, and low carbohydrate) and pharmacologic intervention with oral anti-hyperglycaemic agents, insulin, glucagon-like peptide 1 agonists, and/or lipid-lowering agents. Patients with milder metabolic abnormalities may be effectively treated with such therapies at the start of the disease process. However, the disease is progressive and those with more severe abnormalities often do not respond to these treatments due to the profound nature of their underlying abnormalities, especially when insulin resistance is severe and/or triglycerides are significantly elevated.

Moreover, conventional therapies do not address the underlying leptin deficiency and therefore there is an unmet medical need for a therapy that corrects the underlying pathophysiology of the lipodystrophic state and effectively improves the metabolic disorders in these patients.

3.1.3. Main clinical studies

The primary data in support of the efficacy of metreleptin are derived from the open label Investigator-sponsored Study NIH 991265/20010769. The study was performed by the National Institute of Health (NIH) and data were retrospectively collected. The single-arm open-label design is justified given the rarity of the disease and the fact that the open-label study design afforded the greatest sample population exposure to metreleptin in this rare indication.

The primary objectives of the studies were to determine if metreleptin could be safely administered to patients with LD and to determine if metreleptin would be effective in lowering plasma glucose and lipid abnormalities in patients with this disease.

Study participants were female and male patients with LD, including congenital/familial and acquired forms enrolled on the basis of having low circulating protocol-specified leptin levels and either presence of diabetes mellitus (ADA criteria), fasting insulin concentration >30 µL/mL or fasting TG concentration > 200 mg/dL.

Overall, 107 patients were enrolled, with GL and PL. The PL patient group originally proposed to be eligible for treatment was characterised by leptin levels <12 ng/mL with triglycerides ≥5.65 mmol/L and/or HbA1c ≥6.5%. A separate analysis was made for this subgroup.

The co-primary endpoints were HbA1c and triglyceride levels, which are objective measurements that can be evaluated with a single-arm, baseline-controlled, within patient design. Many subgroup analyses were performed in order to inform on influences of baseline metabolic parameters, age, aetiology of disease, background medication, etc.

No separate dose-response studies were performed. Information to support metreleptin dosage instructions was empirically developed from the long-term efficacy results from Study NIH 991265/20010769.

Supportive data for this application are form Study FHA101. This was a treatment IND study designed to provide metreleptin access to physician-confirmed LD (GL and PL) patients with diabetes mellitus and/or hypertriglyceridaemia with triglycerides >200 mg/dL (however without specific leptin requirements). Design and endpoints were similar to the main study, but overall the metabolic abnormalities of the patients were in general less elevated.

3.2. Favourable effects

In Study NIH 991265/20010769, mean actual change in HbA1c to Month 12/LOCF was -2.2% ($p<0.001$) for GL patients in the full analysis set (FAS) and -0.9% ($p<0.001$) for patients in the FAS in the PL subgroup (characterised by leptin levels <12 ng/mL with triglycerides ≥5.65 mmol/L and/or HbA1c ≥6.5%).

In the same study, mean percent change in triglycerides to Month 12/LOCF was -32.1% ($p=0.001$) for the GL group in the FAS and -37.4% ($p<0.001$) in the FAS PL subgroup (characterised by leptin levels <12 ng/mL with triglycerides ≥5.65 mmol/L and/or HbA1c ≥6.5%) excluding 1 outlying noncompliant patient.

Mean change in fasting plasma glucose (FPG) to Month 12/LOCF was -3.0% ($p<0.001$) for the GL group in the FAS and -1.8% ($p=0.003$) in the FAS PL subgroup (characterised by leptin levels <12 ng/mL with triglycerides ≥5.65 mmol/L and/or HbA1c ≥6.5%).

Nearly 80% of GL patients (FAS) and 68% of patients in the PL subgroup (FAS) 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.

Subgroup analyses by baseline metabolic abnormalities, showed that patients with more abnormal results had greater decreases from baseline in these parameters. Both males and females with GL sustained clinically meaningful and statistically significant reductions in HbA1c and triglycerides at Month 12/LOCF.

Endpoints of supportive study FAG101 confirm results of pivotal study.

3.3. Uncertainties and limitations about favourable effects

The studies were open label, non-randomised and uncontrolled which is challenging to interpret even in an ultra-rare disease with no existing causal therapy. Parameters were compared to corresponding baseline values.

As dietary compliance and calorie-intake were not controlled or not followed, their contribution to the magnitude and maintenance in observed metabolic and other (liver e.g.) effects is not known. There are no data on genetic evaluation of the study populations investigated although several genetic disturbances have been identified so far behind congenital and familial lipodystrophies.

The number of patients is low, and not all endpoints and all time points were measured in a sufficiently large number of patients.

Very few data are available in patients below 6 years of age (5 GL patients, no PL patient). Effect on HbA1c and TG levels in patients below 12 years of age is less pronounced (no PL patient).

No subgroups were made based on BL leptin levels including leptin levels that were originally used for inclusion in studies for men/women.

Subgroup of PL patients for inclusion in the indication was sought with metabolic parameters that cause symptoms that are as severe as in GL patients. However, PL patients did not require to undergo an optimisation period under standardised treatment (antidiabetic, lipid-lowering).

No separate dose finding study was performed and dose-escalation data is gathered from the pivotal efficacy study. Therefore, dosing is based on treatment response.

Given that the product is intended to be administered by the patient himself or by the care giver, there is a risk that the absence of solvent for reconstitution can lead to medication errors.

A blocking activity of metreleptin has been observed *in vitro* in the blood of the majority of patients (96%) but the impact on the efficacy of metreleptin could not be clearly established. Some patients with NAb experienced efficacy loss, but the majority of patients had reversal of NAc during treatment and/or could be managed by dose adaptation.

3.4. Unfavourable effects

The most frequently reported adverse events were weight decreased (15%) hypoglycaemia (13%); fatigue (7%). Other commonly reported adverse events were injection site reaction, neutralising antibodies, decreased appetite, nausea, and alopecia. Six of 148 patients died during the two LD studies. Serious adverse events included abdominal pain and pancreatitis, infections, and worsening liver function.

In both trials only a low number of serious adverse were considered as drug-related: 3 cases in the NIH GL patient group (hypertension, respiratory distress, ACLC) and 1 in the FHA101 overall PL patient group (hypoglycaemia). No drug-related deaths occurred in the LD studies; and overall death rate was also very low (4% across both trials) with no apparent imbalance between LD subgroups or between the trials.

The rate of occurrence of TEAEs was low. Treatment discontinuations due to TEAEs were also low in both LD trials, with 6 patients discontinuing treatment in the NIH study and 4 in the FHA study. Only two of these, one in each study were considered drug-related.

A number of AEs are considered of particular interest due to their known or possible association with metreleptin treatment, namely hypersensitivity, hypoglycaemia, neoplasms (in particular T-cell

lymphomas), hepatic disorders, autoimmune disorders, serious infections, pancreatitis and injection site reactions.

No worrying trends were seen amongst the LD patients in either trial in regards to hypersensitivity events, and only two occurred concurrent with NAb positive immunogenic status.

Metreleptin decreases insulin resistance thereby increasing the possibility that hypoglycaemia events may occur and that adjustments of anti-diabetics may be necessary. Generally reported hypoglycaemia events were mild in severity and no patterns of onset relative to treatment start were seen. Events did not have clinical sequelae, and none of them led to discontinuation of treatment.

Only three cases of T-cell lymphoma were noted across both LD trials, of which two were more likely caused by co-morbid issues rather than treatment. Of note, no T-cell lymphomas were reported in the supportive obesity trials.

Injection site reactions were expectedly noted during the trials, and though the incidence rates varied none led to study discontinuation. Of note is also that fact that more than 50% of events occurred in the first month of treatment, implying that habituation to the injections occurs.

Finally, metreleptin was shown to be immunogenic as 88 % of the 74 patients who had antibody testing in the main and supportive study were positive for ADA – and about 14% of overall LD patients developed a neutralising response.

Based on an FDA request available samples were re-analysed using a receptor binding assay, and this more sensitive test revealed an even higher amount of persons to be ADA and NAb positive (96% and 36% respectively). Despite the higher numbers, no real change in safety profile was apparent following the new analysis, except for a seemingly temporal association of severe/serious infections and NAb formation.

3.5. Uncertainties and limitations about unfavourable effects

Even though TEAEs, had relatively low incidence rates, interpretation of these results is hindered by the overall small number of patients included in the submitted studies (which are further divided in distinct disease-type subgroups) but also the lack of a control arm in the pivotal LD trials, and that the underlying disease has many significant co-morbidities. Further information on the safety profile of the product will be collected.

The effect of leptin (and consequently metreleptin) on cancer growth remains unknown. Endogenous leptin has been shown to increase cell proliferation in different animal and cancer cell models. Cases of T-cell lymphoma have been reported in the metreleptin development programme, and even though metreleptin causality cannot be confirmed, the occurrence of such events in a small safety data-set is of concern. Appropriate wording on this potential risk has been included in the product information and educational material for health-care professionals and patients, and follow-up of patients in the disease registry that is being planned will allow further collection of information on this topic.

A number of pregnancies occurred in LD patients during the trial durations. Given that leptin is implicated in functioning of the hormonal system, affecting amongst others the release of LH, it is to be expected that metreleptin treatment may restore of improve fertility in patients and this is reflected in the product information. Unplanned pregnancy is also included in the RMP as an important potential risk, and is one of the topics of interest in the disease registry.

Only a subset of LD patients had ADA data available, thus it is not possible to estimate the precise rate of ADA positive patients or the associated adverse reactions from the current data. Moreover,

given the very high reported rates of patients with ADA and the discrepancies between the assays used there are some questions over the reliability of methods used to detect ADAs.

A potential risk of ADA is NAb cross-reacting with endogenous leptin, especially in the PL population, leading to loss of activity in these patients. A temporal association also seems to exist between formation of NAbs and occurrence of severe/serious infections. Though no causality has been confirmed, it is theoretically possible that these events are the consequences of the mechanism of the underlying illness in conjunction with the immune suppressive effect of NAbs. In order to address these uncertainties around immunogenicity the applicant will provide an integrated immunogenicity report, using validated assays and analysing samples from previous and future studies with metreleptin.

3.6. Effects Table

Table 52. Effects Table for Myalepta name in the treatment of congenital or acquired generalised lipodystrophy and familial or acquired partial lipodystrophy (data cut-off: 26 March 2014).

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects- Congenital or acquired generalised lipodystrophy					
HbA1c	Mean change from baseline at month 12	N/A (SD)	-2.2 (2.15), P<0.001	Effect confirmed in different analysis data-sets Dose determined by prescriber	NIH 991265/20010769 (FAS)
TG			32.1 % (71.28) p<0.001		
Favourable Effects- Familial or acquired partial lipodystrophy					
HbA1c	Mean change from baseline at month 12	N/A (SD)	0.9 (1.22), p<0.001	Effect confirmed in different analysis data-sets Dose determined by prescriber	NIH 991265/20010769 (FAS)
TG			-37.4 (30.81) p<0.001		
Unfavourable Effects					
Pancreatitis		%	4.5	Higher rates reported before treatment, underlying condition linked with these AEs	NIH 991265/20010769
Hypoglycaemia		%	15		NIH 991265/20010769
T-cell lymphoma		N	3	Small number of cases, difficult to assess causality	NIH 991265/20010769
ADA NAb	ADA (Nab) positive at any stage post-treatment	%	ADA: 87.8 (96.1**) Nab: 13.5 (37.3**)	Not all patients had known ADA status **Numbers obtained with more sensitive receptor binding assay	Pooled : NIH 991265/20010769 FHA101

Abbreviations: HbA1c: glycated haemoglobin (A1c), SD: Standard Deviation, FAS: Full Analysis Set. TG: Triglycerides, ADA: Anti-Drug Antibodies, Nab: Neutralising Antibody

Notes: PL subgroup = patients with BL HbA1c≥6.5% and/or TG≥5.65 mmol/L, (*): excluding TG result for one outlier patient

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The severe metabolic abnormalities in patients with LD are often difficult to control even with high doses of currently available diabetes and lipid-lowering therapies. There is a significant unmet medical need for a replacement therapy that effectively improves the metabolic disorders in these ultra-rare patients that have metabolic abnormalities despite receiving these type of medications. Not only are these treatments rendered less effective by the profound insulin resistance, they also do little to correct the pathophysiological mechanisms underlying their development.

The treatment is not directly addressing the underlying cause of the disease, but is replacing leptin hormone deficiency that results from the lack of adipose tissue. Replacement of low or missing leptin by recombinant analogue is handling one main pathophysiological factor, but downstream signalling may still remain defective in some cases.

As an analogue of leptin, it was anticipated that metreleptin would improve the metabolic abnormalities associated with leptin deficiency in patients with lipodystrophy, i.e., reduce HbA1c and triglycerides. Actual change in HbA1c is consistent with improvement in insulin sensitivity, and clinically meaningful and statistically significant improvements were obtained in the pivotal study for both GL and (a subgroup of) PL patients. Clinically meaningful and statistically significant improvements in hypertriglyceridaemia were also obtained, again in both groups of patients.

Subgroup analysis according to metabolic parameters at baseline showed that patients with more severe baseline parameters in HbA1c/TG have greater decrease from baseline.

Most drug-related TEAEs observed could be expected based on the nature of treatment and the co-morbidities of the target population. Immunogenic events, hypoglycaemia, T-cell lymphomas and injection site reactions are of most interest, and their rate of occurrence was generally low.

Submitted trials showed very low number of serious adverse events that could be considered as drug-related. No worrying trends were seen amongst the LD patients in either trial with regards to hypersensitivity events, and only two occurred concurrent in the presence of NAb. ADA positivity of any type did not appear to have an impact on the safety profile of the patient. Antibodies to metreleptin were detected in high, nearly 90% of patients, and almost 10% of them were neutralising which might lead to loss of efficacy but also may block the remaining endogenous leptin in PL. This is of concern as leptin has several, even not completely understood functions in addition to its role in appetite and energy regulation.

Metreleptin increases insulin resistance thereby increasing the possibility that hypoglycaemia events may occur and that adjustments of anti-diabetics may be necessary. Generally incidence were mild in severity and no patterns of onset relative to treatment start were seen. Likewise, none of the hypoglycaemic event noted had clinical sequelae, and none led to discontinuations. The majority of events could also be controlled by dietary means and required no adjustment of glycaemic medications.

Finally, sudden discontinuation of metreleptin treatment may cause rebound phenomena manifested as severe bouts of pancreatitis, and thus tapering off the dosing of metreleptin is recommended. This risk will be minimised through a tapering period of two weeks.

3.7.2. Balance of benefits and risks

Despite the limitations of the submitted data arising from the rarity and heterogeneity of the

disease, and the retrospective analysis of data, the clinically meaningful, and statistically significant, and sustained decreases in HbA1c and triglycerides demonstrate clear efficacy of treatment.

The reported results are even more significant in the context of the very high unmet medical need in patients with lipodystrophy that experience severe metabolic syndromes that cannot be adequately controlled with available antidiabetic and lipid-lowering therapies.

Safety data did not reveal any unexpected adverse events however there are several uncertainties around the use of the product due to limited size of the safety database, the lack of a control arm in the studies, the multiple co-morbidities of the target population which render causality assessment challenging as well as the lack of a reliable anti-drug antibody detection method. The uncertainties have been addressed by appropriate warnings in the product information and additional risk minimisation activities to better inform the treating physician and patients of the risks associated with metreleptin use. Furthermore, a number of additional pharmacovigilance activities, such as the disease registry and a thorough immunogenicity investigation are expected to provide additional information to better characterise the safety profile of metreleptin.

In patients with confirmed congenital or acquired generalised LD (Berardinelli-Seip syndrome and Lawrence syndrome) the beneficial effects of metreleptin clearly outweigh any potential risks. These patients are the ones with the highest need for treatment and with negligible, if any at all, levels of endogenous leptin. Despite the limited available data in paediatric patients the CHMP acknowledged that GL paediatric patients above 2 years of age can benefit from treatment with metreleptin as these patients present at a very young age with metabolic abnormalities and hepatomegaly, complications of micro- and macrovascular disease, as well as progressive liver disease.

Within the familial partial LD or acquired partial LD (*Barraquer-Simons syndrome* population there is a sub-group of patients which are adequately controlled with adjusted diet, antidiabetic and lipid lowering therapy. Moreover, as these patients have some endogenous leptin there is the theoretical risk of cross reaction with Nab, though this was not observed in this patient population.

Therefore, in the PL indications it is considered appropriate to restrict use only to those for whom standard treatments have failed to achieve adequate metabolic control. Furthermore as there are no data available for this type of LD for patients under 12 years of age, use of the product should be limited to adults and children 12 years of age and above

The uncertainties have been addressed by appropriate warnings in the product information and additional risk minimisation activities to better inform the treating physician and patients of the risks associated with metreleptin use. Furthermore, a number of additional pharmacovigilance activities, such as the disease registry a through immunogenicity investigation are expected to provide additional information to better characterise the safety profile of metreleptin.

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely. As a consequence the sample population available for inclusion in clinical trials is extremely limited and therefore the applicant cannot reasonably be expected to provide comprehensive evidence.

Therefore, in light of the positive benefit/risk and considering the rarity of the indications, and the limited evidence available, recommending a marketing authorisation under exceptional circumstances is considered appropriate subject to the following specific obligations:

- The applicant is required to set up a lipodystrophy disease registry In order to characterise the treatment of patients with metreleptin and to evaluate the long-term safety and effectiveness under conditions of usual clinical practice metreleptin;
- The applicant is required to conduct an efficacy study in order to further characterise the effect of metreleptin on poor metabolic control once background therapy is maximised in patients with partial lipodystrophy;
- The applicant should provide an integrated immunogenicity report using validated assays for the detection of anti-drug antibodies from all available data in order to further investigate the clinical significance of the immunogenicity of metreleptin (ADAs and NAbs)

3.8. Conclusions

The overall benefit-risk of Myalepta is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Metreleptin is favourable in the following indication:

adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

- with confirmed congenital generalised LD (*Berardinelli-Seip syndrome*) or acquired generalised LD (*Lawrence syndrome*) in adults and children 2 years of age and above
- with confirmed familial partial LD or acquired partial LD (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of MYALEPTA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness among healthcare professionals and patients/carers about the important risks contained in the Risk Management Plan. It is also aimed to guide prescribers about the appropriate management of these risks.

The MAH shall ensure that in each Member State where MYALEPTA is marketed, all healthcare professionals and patients/carers who are expected to use MYALEPTA are provided with the following educational package:

- Healthcare professionals educational material
- Patients/carers educational material

  Healthcare professionals' educational material should contain:

  - The Summary of Product Characteristics
  - Guide for healthcare professionals
  - Healthcare professionals training material
  - A dose card on which the doctor can write for the patient the dose in mg, ml (and where appropriate units from a 0.3 ml U100 insulin syringe). This card will also include pictures of the relevant syringe sizes on which the doctor can draw a line to indicate on the volume of water for injection to use for reconstitution and the volume of reconstituted solution to inject.

The **Guide / training material for healthcare professionals** shall contain the following key elements:

- Reminders on key prescribing information content, including indicated population, posology, warnings and precautions, and other safety- related information which is key to safe use of the product. This will include for example instructions for handling possible ADRs.
- Responsibility of the prescribing physician to provide appropriate training to the patient/carer who will administer the treatment and that the first dose should be administered in the presence of a doctor or nurse.
- The requirement to perform regular follow-ups with the patient/carer to ensure continued correct and compliant MYALEPTA reconstitution and treatment.
- Hypersensitivity has been reported with MYALEPTA use including anaphylaxis, urticaria and generalised rash. If an anaphylactic reaction or other serious allergic reaction occurs, administration of MYALEPTA should be permanently discontinued immediately and appropriate therapy initiated.
- Non-compliance with or abrupt withdrawal of MYALEPTA may result in worsening of hypertriglyceridaemia and associated pancreatitis:
  - Risk factors include patients with a history of pancreatitis or severe hypertriglyceridaemia.
  - Tapering the dose over a two-week period is recommended in conjunction with a low fat diet.
  - Patients should be monitored during tapering. Initiating or adjusting lipid lowering medications may be required.
  - Signs and/or symptoms consistent with pancreatitis should prompt an appropriate clinical evaluation.
- Hypoglycaemia with concomitant use of insulin and other antidiabetics may occur:
  - Large dose reductions of 50% or more of baseline insulin requirements may be needed in the first 2 weeks of MYALEPTA treatment. Once insulin requirements have stabilised, dose adjustments of other anti-diabetics may also be needed in some patients.
  - Monitoring of blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogues and combination treatment is warranted. Patients and carers should be advised to be aware of the signs and symptoms of hypoglycaemia.
  - In case of hypoglycaemic events of a non-severe nature, food intake management may be considered as an alternative to dose adjustment of anti-diabetics.
  - Rotation of injection sites is recommended in patients co administering insulin (or other SC medicinal products) and MYALEPTA.
- Ways to prevent the occurrence of medication errors
  - MYALEPTA is administered by SC injection and proper technique should be used to avoid intramuscular injection in patients with minimal SC tissue.
  - HCPs should provide training to patients on the correct technique.

- Patients and/or caregivers should prepare and administer the first dose under the supervision of a qualified HCP.
- Detailed instructions for use.
- Guidance in the educational materials on:
  - The size of syringes and needles to prescribe
  - Prescribing the dose in both mg and ml and, where a 0.3mL U100 insulin syringe is used, informing patients on the dose in "units" on the syringe to inject
  - The prescribing of ampoule/vial sizes volumes of water for injection in appropriate volumes to reduce the risk of re-use

Pharmacists will be guided in the educational materials on the ancillary items that need to be dispensed to patients including appropriate sized reconstitution and administration syringes and needles, appropriate sized vials/ampoules of water for injection, alcohol swabs and a sharps bin plus how to access Aegerion reconstitution and administration kits containing all of the above items except the water for injection and sharps bin.

- Access to further materials, including training videos in multiple languages that will demonstrate each step to in preparing and administering MYALEPTA via a website.

o T-cell lymphoma

- Acquired LDs are associated with autoimmune disorders. Autoimmune disorders are associated with an increased risk of malignancies including lymphomas.
- Lymphoproliferative disorders, including lymphoma have been reported in patients with acquired generalised LD not treated with MYALEPTA. Cases of T-cell lymphoma have been reported in clinical studies in patients taking MYALEPTA. A causal relationship between lymphoma and MYALEPTA has not been established.
- The benefits and risks of MYALEPTA should be carefully considered in patients with acquired LD and/or those with significant haematologic abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma and/or lymphadenopathy). An association between the development of NAbs and serious and severe infections cannot be excluded and the continuation of MYALEPTA should be at the discretion of the prescriber.

o MYALEPTA may increase fertility, due to effects on LH and thus the chances of unplanned pregnancy. Women of childbearing potential should be advised that MYALEPTA may increase fertility and should be encouraged to use contraception.

o Neutralising antibodies may develop on MYALEPTA therapy. An association between the development of neutralising antidrug antibodies and serious and severe infections cannot be excluded, and, continuation of MYALEPTA should be at the discretion of the prescriber. Consideration should also be given by the prescriber to have patients tested for the presence of neutralising antibodies.

o Loss of efficacy, potentially due to neutralising antibodies, may occur in patients on MYALEPTA therapy. While the impact of neutralising antibodies on efficacy has not been confirmed, consideration should be given by the prescriber to have patients tested for the presence of neutralising antibodies if there is significant loss of efficacy despite MYALEPTA administration.

Patients/carers educational material should contain:

- The patient information leaflet
- Guide for patients/carers
- Patients/carers training material

  The **Guide/training material for patients/carers** shall contain the following key elements:

  - Reminders on key prescribing information content, including indicated population, posology, warnings and precautions, and other safety- related information which is key to safe use of the product. This will include for example instructions for handling possible ADRs
  - Allergic reactions can occur with MYALEPTA use. Advice will be provided on symptoms of an allergic reaction and action to be taken in the event of such a reaction.
  - The need of compliance with treatment due to the risk of pancreatitis when medication is abruptly stopped. The importance of tapering the dose of MYALEPTA over two weeks if it is to be discontinued.
  - Hypoglycaemia with concomitant use of insulin and other antidiabetics may occur.
  - The risk of medication error:
    - Responsibility of the prescribing physician to provide appropriate training to the patient/carer who will administer the treatment and that the first dose should be administered in the presence of a doctor or nurse
    - The requirement to perform regular follow-ups with the patient/carer to ensure continued correct and compliant MYALEPTA reconstitution and treatment
    - Guidance on the appropriate syringe size ancillary administration set to prescribe according to the dosage of MYALEPTA and how to read the syringe volumes
    - How to access a video on line which shows step by step how to reconstitute, measure the correct dose and administer it subcutaneously
  - The association between LD and lymphoma and that the patient will be monitored during treatment.
  - Serious and severe infections secondary to the appearance of NAb may occur.
  - MYALEPTA may increase fertility, due to effects on LH and thus the chances of unplanned pregnancy.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to further evaluate the long-term safety and effectiveness of Myalepta under normal conditions of clinical practice, the applicant should establish a registry including all patients with generalised or partial lipodystrophy treated with Myalepta according to an agreed protocol.	Draft protocol to be submitted 6 months after notification of the European Commission decision Annual reports to be submitted as part of the annual re-assessment
In order to further investigate the effect of Myalepta on poor metabolic control once background therapy is maximized in patients with familial or acquired partial LD, the applicant should conduct an efficacy and safety study according to an agreed protocol.	Draft protocol to be submitted 3 months after notification of the European Commission decision The final study report should be submitted by 2022
In order to address the potential safety concerns and/or lack of efficacy related to immunogenicity of Myalepta, the applicant should submit an integrated analysis of immunogenicity measured according to validated assays. The Applicant should conduct this integrated analysis according to an agreed protocol including samples from all available historical samples from previous studies (NIH991265/20010769, FHA 101, NASH4 and obesity studies) with patients with GL/PL and samples obtained from patients that will be included in the efficacy and safety study in PL patients, the paediatric investigational plan (PIP) study and the patients registry.	Draft protocol to be submitted 3 months after notification of the European Commission decision The final study report should be submitted by 2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that metreleptin is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0314/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

4.1. Conclusions

The overall benefit-risk of Metreleptin is positive.