SIGNATURE PAGE

Document Code: CLI-METREAA1-01-APP 16.1.1-05644
Title: AEGR-734-400_MEASuRE_Protocol_V11.0_08June2026
Version: 3.0,CURRENT
Status: Approved, since: 22-Jun-2026 08:08:29 UTC

Electronic Signature:
Signed by: Fuchs Orenbach Shir (S.FUCHS)
Date: 12-Jun-2026 09:36:26 UTC
Meaning of Signature: Clinical Approval

Signed by: Furness Hugh (HUGHFURNESS)
Date: 17-Jun-2026 13:16:05 UTC
Meaning of Signature: Medical Approval

Signed by: Garavaglia Daniela (USR03808)
Date: 22-Jun-2026 08:08:25 UTC
Meaning of Signature: Statistician Approval

Note: Each electronic signature above is equivalent to a handwritten signature since the computer system managing the electronic document fully complies with the international rules (i.e. FDACFR21part11, EU Annex11) concerning Electronic Records and Electronic Signatures Management.

MEASuRE:
METRELEPTIN EFFECTIVENESS AND SAFETY REGISTRY

Protocol Number:	AEGR-734-400
Version/Date:	11.0 / 08 June 2026
Name of test drug:	Metreleptin
Sponsor:	Chiesi Farmaceutici S.p.A Via Palermo 26/A 43122 Parma - Italy Phone: +39 0521 2791
Medical Contact:	Dr. Shir Fuchs Orenbach Clinical Program Lead

SYNOPSIS/ REGISTRY INFORMATION

Title	**MEASURE: METRELEPTIN EFFECTIVENESS AND SAFETY REGISTRY**
Protocol version identifier	AEGR-734-400: Version 11.0
Date of protocol	08 June 2026
Active substance	Metreleptin
Medicinal product	Myalept in US / Myalepta in EEA
Product reference	EMEA/H/C/004218
Procedure number	EEA: SOB001 US: PMR 2456-1
Marketing Authorization Holder	Chiesi Farmaceutici S.p.A.
Research question and objectives	The registry is designed to evaluate the long-term safety and effectiveness of metreleptin under normal conditions of clinical practice. The objectives of the registry are: <u>Primary objectives</u> • To determine the incidence and severity of the following safety events in patients prescribed metreleptin in normal clinical practice: • Acute pancreatitis associated with the discontinuation of metreleptin; and all cases of fatal or necrotizing pancreatitis • Hepatic adverse events • Hypoglycemia stratified by severity and concomitant antidiabetics dose modifications • Hypersensitivity reactions • Serious and severe infections, including serious infections resulting in hospitalization and death • Loss of efficacy, potentially due to anti-drug antibodies (ADAs) with blocking activity • New diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis) • Exacerbation of existing autoimmune disorders • All cancers (excluding non-melanoma skin cancer) by cancer type

	• Exposed pregnancies and pregnancy outcomes stratified by planned or unplanned • All-cause deaths (including causes of death) • Medication errors <u>Secondary Objectives</u> • To describe the overall demographic and clinical characteristics, and metreleptin exposure in all patients treated with Metreleptin (pattern of use analysis) • To describe routine laboratory measurements that could be inferred as effectiveness endpoints (including Hemoglobin A1c [HbA1c], fasting plasma glucose [FPG], and triglycerides [TG]) over time <u>Exploratory Objectives</u> • Use in pregnancy and lactation • Use in elderly • Effect of metreleptin on brain development • Effect of metreleptin on bone metabolism • Effect of metreleptin on sexual maturation (Tanner staging) • Neuroendocrine parameters and levels of the following hormones: testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH) and free triiodothyronine (T3) and thyroxine (T4) • Contingent on study sample size, the study will also estimate the incidence rate of the primary outcomes of interest by patient characteristics. • In patients with results from immunogenicity testing, the incidence of ADAs with blocking activity will be estimated.
Country(ies) of study	Patients will be enrolled from (but not limited to) the European Economic Area (EEA) and the United States
Author	Lori Hartnett Senior Clinical Project Manager

MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder(s)	Chiesi Farmaceutici S.p.A, Via Palermo 26/A, 43122 Parma, , Italy.
Marketing Authorization Holder (MAH) contact person	For EEA: Siobhán Moyna Chiesi Farmaceutici S.p.A Via Palermo 26/A 43122 Parma - Italy Email: siobhan.moyna@chiesi.com For US: Shivani Choudhary Chiesi USA, Inc. 175 Regency Woods Place Suite 600, Cary, NC 27518 Telephone: +1-617-637-6836 Email: shivani.choudhary@chiesi.com

INVESTIGATOR AGREEMENT

I have read this protocol for Chiesi Farmaceutici S.p.A AEGR-734-400 MEASuRE: Metreleptin Effectiveness and Safety Registry.

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representatives.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorization from Chiesi Farmaceutici S.p.A. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that Chiesi Farmaceutici S.p.A may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Chiesi Farmaceutici S.p.A.

Signature: _____ Date: _____

1 TABLE OF CONTENTS

List of Tables

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADAs	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AGL	Acquired generalized lipodystrophy
ALT	Alanine aminotransferase
APL	Acquired partial lipodystrophy
AST	Aspartate aminotransferase
CGL	Congenital generalized lipodystrophy
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
EA	Endpoint adjudication
EAC	Endpoint adjudication committee
eCRF	electronic case report form
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
EEA	European Economic Area
ER	Emergency room
FPL	Familial partial lipodystrophy
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GL	Generalized lipodystrophy
GPP	Good Pharmacoepidemiology Practices
HbA1c	Hemoglobin A1c
HCP	Healthcare provider
HDL-C	High density lipoprotein- cholesterol
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	Definition
ISPE	International Society for Pharmacoepidemiology
LD	Lipodystrophy
LDL-C	Low density lipoprotein-cholesterol
LH	Luteinizing hormone
LOCF	Last observation carried forward
MACDP	Metropolitan Atlanta Congenital Defects Program
MA	Marketing Authorization
MAH	Marketing Authorization Holder
mg/dL	Milligram per deciliter
mmol/L	Millimole per liter
ng/mL	Nanogram per milliliter
NIH	National Institute of Health
PL	Partial lipodystrophy
PT	Prothrombin time
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
TG	Triglycerides
T3	Triiodothyronine
T4	Thyroxine
US	United States

3 RESPONSIBLE PARTIES

The Sponsor, Chiesi Farmaceutici S.p.A is responsible for providing reasonable resources for study implementation and assuring study progress. They are also responsible for designing the study in a manner that meets regulatory and methodological standards, conducting analyses and preparing scientific reports.

4 ABSTRACT

Title	**MEASURE: METRELEPTIN EFFECTIVENESS AND SAFETY REGISTRY**
Rationale and background	In the clinical development program, 148 patients with generalized (GL) or partial (PL) lipodystrophy (LD) were exposed to metreleptin. Based upon data from these patients, the risk management plan was developed in which important identified risks, important potential risks and missing information were defined. In line with the conditions of the marketing authorization (MA), this observational registry will seek to further characterize these safety concerns in routine clinical practice. In addition, it will also seek to further characterize effectiveness in the same setting.
Research questions and objectives	The registry is designed to evaluate the long-term safety and effectiveness of metreleptin under normal conditions of clinical practice. **Primary Objectives** To determine the incidence and severity of the following safety events in patients prescribed metreleptin in normal clinical practice: • Acute pancreatitis associated with the discontinuation of metreleptin; and all cases of fatal or necrotizing pancreatitis • Hepatic adverse events • Hypoglycemia stratified by severity and concomitant antidiabetics dose modifications • Hypersensitivity reactions • Serious and severe infections, including serious infections resulting in hospitalization and death • Loss of efficacy, potentially due to anti-drug antibodies (ADAs) with blocking activity • New diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis) • Exacerbation of existing autoimmune disorders • All cancers (excluding non-melanoma skin cancer) by cancer type • Exposed pregnancies and pregnancy outcomes stratified by planned or unplanned • All-cause deaths (including causes of death) • Medication errors **Secondary Objectives** • To describe the overall demographic and clinical characteristics, and metreleptin exposure in all patients treated with metreleptin (pattern of use analysis)

	• To describe routine laboratory measurements that could be inferred as effectiveness endpoints (including glycated hemoglobin [HbA1c], fasting blood glucose [FPG], and triglycerides [TG]) over time **Exploratory Objectives** • Use in pregnancy and lactation • Use in elderly • Effect of metreleptin on brain development • Effect of metreleptin on bone metabolism • Effect of metreleptin on sexual maturation (Tanner staging) • Neuroendocrine parameters and levels of the following hormones: testosterone, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH) and free T3 and T4 • Contingent on study sample size, the study will also estimate the incidence rate of the primary outcomes of interest by patient characteristics. • In patients with results from immunogenicity testing, the incidence of ADAs with blocking activity will be estimated.
Study design	This is a non-interventional, multicenter, prospective, observational study of patients initiating treatment with metreleptin for lipodystrophy in the US and EEA. Voluntary participation of countries in the registry will depend on market uptake of metreleptin.
Population	Patients with generalized or partial lipodystrophy being treated with metreleptin as a result of prescribing in routine clinical practice.
Variables	Baseline demographics, medical history and comorbidities at the time of initiation of metreleptin, medication history including concomitant medications, details regarding metreleptin therapy, and laboratory tests will be collected. Thereafter, at all follow-up visits, after the initiation of commercial metreleptin, the following information will be collected: vital status, changes in metreleptin treatment, reasons for the change or reason for discontinuation, changes in concomitant medications, AEs, SAEs, and laboratory tests.
Data sources	Standardized data collection forms will be designed to gather the data from routine clinical practice visits. All governing codes of ethics and regulations that guide ethical collection of patient data will be followed.
Study size & Enrolment	In the US, the registry will offer enrolment to all patients treated with metreleptin until at least 100 patients have been enrolled. In the EEA, the registry will offer enrolment to all patients treated with metreleptin. All patients will be followed for a minimum of 10 years (US) or the duration of the lifecycle of the product (EEA) unless they withdraw consent to participate in the registry or die.
Data analysis	Descriptive statistics will be presented. No formal hypothesis testing will be performed.
Milestones	Submission of full protocol within six months of European Commission Decision.

	Annual interim reports will be provided to the agency including a listing of reported events, incidence rates (as expressed in number of events per patients-years) and other relevant statistical parameters for the duration of the study (10 years from last patient enrolled in the US; for the duration of the lifecycle of the product in the EEA).

5 DOCUMENT HISTORY AND SUMMARY OF CHANGES OF CURRENT AMENDMENT

DOCUMENT HISTORY BY REGION

AEGR-734-403 (SOB001; EU MEASuRE)

Version Number	Date	Comments
1	29Jan2019	Initial protocol
2	05Jul2019	Update
N/A	01Feb2021	Retired

AEGR-734-400 (V 1 – V 6: US MEASuRE; FROM V 7: GLOBAL MEASuRE)

Version Number	Date	Comments
1	15 Jan 2014	Initial (Not Implemented)
2	10 Dec 2014	Update (Not Implemented) Also referred to as Revision 1.
3	06 Feb 2015	Update (Not Implemented) Also referred to as Revision 2.
3	04 May 2015	Update (Not Implemented) In error, this version was referred to as V 3.0.
4	22 Oct 2015	First protocol version which was implemented
5	04 Jan 2017	Update (Not Implemented)
6	11 May 2017	Update implemented
7	01 Feb 2021	Update – submitted to FDA Incorporates approved EU protocol v2 (AEGR-734-403) to create the harmonized global MEASuRE protocol as notified to the EMA via the Annual re-assessment
7.1 – FDA 8.0 – EEA	19 July 2021	V7.1 submitted to FDA Minor amendment in EEA. Not submitted to EEA. Submitted to country level Regulatory Authorities
8.1	20 Oct 2021	Update – submitted to FDA as v7.2 following comments on 7.1. then finalized as v8.1 in line with EEA protocol. Minor amendment in EEA. Not submitted to EMA or country level Regulatory Authorities.

Version Number	Date	Comments
8.2	14 Dec 2021	Non substantial amendment in US or EMA. No submission to FDA or EEA. Submission to IRBs and country level Regulatory Authorities and ECs planned.
8.3	10 Apr 2025	Update submitted to FDA. Non substantial amendment in EEA. Not submitted to EEA.
9.0	17 Nov 2025	Substantial amendment Update submitted to FDA and EEA. Approved by FDA but not implemented as not approved by EMA.
10.0	25 Feb 2026	Non-Substantial Amendment to incorporate EMA feedback regarding registration of the study in the HMA-EMA Catalogue of Real-World Data studies. Not implemented.
11.0	08 Jun 2026	Substantial Amendment to incorporate EMA feedback to revert the Safety Reporting requirements as per the approved Protocol V8.3, Section 11. Update to be submitted to FDA and EEA.

Amendment no. 11.0 (Global), dated 08 June 2026

This summarizes all key changes between protocol v8.3 and protocol v11.0 following the EMA review cycle.

Section Number and Name	Summary of Changes	Reason/Rationale
7 Rationale and Background	• Update loss of efficacy	• To provide most up-to-date information
9.1 Study Design 11 Management and Reporting of Adverse Events/Adverse Reactions	• Cross reference to EAC charter throughout as relevant • Add definitions including ADR and Events of Special	• For clarity
9.2.1 Study Population 9.7.1 Data Analysis for New and Prevalent Users	• Add definition of prevalent current and prevalent prior user	• To align with information presented in the Annual Reports per FDA request
9.2.2 Patient Consent	• Provide process when consent cannot be obtained at the clinic	• Outline remote consent process

Section Number and Name	Summary of Changes	Reason/Rationale
9.2.7 Immunogenicity Assessment	• Clarify process for ADA sample collection	• To align with current best practices
9.4.1 Study Data Acquisition	• Clarify exception for data collection for prevalent metreleptin users	• For clarity
9.4.1.3 Pregnancy and Pregnancy Outcomes	• Clarify pregnancy data collection (footnote of Table 3)	• For clarity
9.7 Data Analysis 10.2 Confidentiality of Study Data	• State that the Sponsor may integrate MEASuRE data with data from other metreleptin studies	• To enhance the Sponsor's knowledge on the effect of metreleptin in lipodystrophy patients for scientific purposes
9.7.1 Data Analysis for New and Prevalent Users 9.7.8 Censoring Criteria	• Clarify process for data collection and for the analysis of prevalent current and prevalent prior user cohorts. Specifically, if the ≥10% threshold is met, the Sponsor will further stratify the prevalent user cohort by prevalent prior users and prevalent current users • Update to avoid duplication. Withdrawal data are captured in the last data collection point	• To align with information presented in the Annual Reports • Updated to avoid duplication
9.8.4 Registration of Study on Public Website	• Update to include clinicaltrials.gov and HMA-EMA Catalogue of Real-World Data studies	• V9.0: The MEASuRE registry is not registered on ENCePP. Furthermore, ENCePP has now transitioned to EMA and registration is not mandatory for MEASuRE since it is not a PASS study. • V10.0: Registration on HMA-EMA Catalogue added to V10.0 per EMA request.
10.2 Confidentiality of Study Data	• Update	• Alignment with UK protocol clarification letter
General	• Update Sponsor name to Chiesi Farmaceutici S.p.A • Minor change to the process of collecting information for patients whose vital status remains unknown • Update immunogenicity program name to Global Immunogenicity Program • Clarify that the Periodic Safety Update Report will be reported per European Union reference dates • Use US spelling throughout • Minor clarification (e.g., for EEA only year of birth will be collected)	• Due to Chiesi acquisition • For clarity and accuracy

Section Number and Name	Summary of Changes	Reason/Rationale
	• Minor updates including typo correction, formatting • Update list of abbreviations • Update reference section	

6 MILESTONES

MILESTONE	PLANNED DATE
Start of data collection	US: Q1 2017 EEA: Q4 2021
End of data collection	US: 10 years from 100th patient enrolled (anticipate Sep 2031) EEA: Not applicable
Annual reports	Annually during the life of the registry.
Final Report of Study Results	US: March 2032 EEA: Open

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

Lipodystrophy (LD) syndromes are clinically heterogeneous inherited or acquired disorders characterized by a common clinical phenotype of selective, variable and often progressive loss of adipose tissue, primarily subcutaneous fat (Garg, 2004; Chan, 2010), combined with a range of metabolic abnormalities associated with a relative deficiency of leptin, a hormone which is normally secreted by adipose tissue. The loss of adipose tissue is variable and may be generalized or restricted to limited areas (partial) with sparing or even accumulation of excess adipose tissue in certain regions (for example around the face and neck in Dunnigan's syndrome).

A framework for classification of LD syndromes has been described based on the underlying aetiology (inherited or acquired) as well as the extent of fat loss (generalized or partial) (Garg, 2004; Chan, 2010). This approach results in four major LD subtypes:

- Congenital generalized LD (CGL)
- Familial partial LD (FPL)
- Acquired generalized LD (AGL)
- Acquired partial LD (APL)

Since LD syndromes are so rare, accurate epidemiology estimates are not available. According to a recent review, the prevalence is currently estimated to be 1.3 to 4.7 cases/million, at the lower range of previously established numbers of ~0.1 to 90 cases/million (Chiquette, 2017). These prevalence estimates were demonstrated through a search of five electronic medical record databases and four literature searches (Chiquette, 2017). However, the actual rate of diagnosis (versus reporting) is unknown, and it is possible that the disease may be under diagnosed, particularly partial forms which affect only parts of the body.

Even though there is considerable heterogeneity in LD syndromes with variable presentations and different mechanisms by which fat loss can occur, all share the unifying feature of loss of subcutaneous (SC) adipose tissue. The loss of adipose tissue results in metabolic abnormalities that are typically more severe than those associated with obesity (Chan, 2010). The lack of normal depots for storage of ingested fats results in hypertriglyceridemia, which is often severe (with serum TGs often elevated in the range of 1000s versus an upper limit of normal of 150 mg/dL in adults) and refractory to treatment with conventional lipid lowering agents.

Deposition of fat occurs in ectopic locations such as liver and muscle, leading to extreme insulin resistance and often to diabetes that is difficult to control, even with high doses of insulin. The accumulation of fat in the liver can cause marked hepatomegaly and steatohepatitis. Because of the loss of adipose tissue, levels of the adipocyte secreted hormone leptin are low. The relative leptin deficiency observed in this disease state also contributes to hyperphagia, which further exacerbates the metabolic abnormalities as patients are driven to ingest more fat than they are able to dispose. As a result, LD is often associated with a range of severe and progressive metabolic abnormalities (e.g., hypertriglyceridemia, insulin resistance, diabetes, and/or liver dysfunction that can result in a high prevalence of end-organ complications and co morbidities which can be life-threatening such as acute pancreatitis, steatohepatitis and cirrhosis, cardiomyopathy, accelerated atherosclerosis, accelerated renal disease.

Myalept (metreleptin) was approved in the United States (US) in 2014 as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy (MYALEPT® USPI). Myalept was also licensed in Japan in March 2013 for the treatment of LD.

In July 2018, Myalepta (metreleptin) was granted a MA in the EEA under exceptional circumstances as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy patients:

- with confirmed congenital generalized LD (Berardinelli-Seip syndrome) or acquired generalized 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.

7.2 CLINICAL STUDIES SUPPORTING METRELEPTIN APPROVAL

The pivotal efficacy data supporting the approval of metreleptin in the EEA was from study NIH 991265/20010769 with supportive data provided by study FHA101. Study NIH 991265/20010769 was an open-label, single-arm, investigator-sponsored study designed to examine whether treatment with metreleptin could improve the metabolic sequalae, including pathological derangements in glucose and lipid homeostasis, found in patients with LD syndromes.

Overall, 107 patients with this ultra-rare disease were enrolled and treated across Study NIH 991265/20010769. A total of 66 patients had GL and 41 had PL, including 31 patients who were included in the PL subgroup, i.e., those PL patients who have similar metabolic disturbances as patients with GL and who were defined as patients with baseline HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L. Most of the patients had the congenital/familial form of the disease including 68% of patients with GL and 87% of patients in the PL subgroup.

Among the 66 patients with GL in the pivotal study, 77% were female with Caucasians representing 47% of the overall study population, Blacks 24%, and other races/ethnicities comprising 29%. Median age of the GL group was 15 years with 68% of patients <18 years of age. The median baseline leptin concentration was 1.0 ng/mL for the 64 patients with data available. In the PL subgroup, all but one of the 31 patients was female and the majority were Caucasian (84%). Patients in the PL subgroup were older (median age 38 years) compared with patients in the GL group, with 84% ≥18 years of age. As expected, median leptin concentration in this subgroup was higher (5.9 ng/mL) than that reported for GL patients.

The supportive Study FHA101 had a similar study design to the pivotal study as it was also an open-label, single-arm clinical trial designed to evaluate the safety and efficacy of metreleptin in patients with GL and PL. As this was a treatment Investigational New Drug study, only HbA1c, glucose, triglycerides, and liver function tests were evaluated for efficacy. Among the 41 patients enrolled and treated in Study FHA101, nine patients had GL and 32 had PL; all patients were from the US. The PL subgroup, i.e., those PL patients with baseline leptin levels <12.0 ng/mL, HbA1c ≥6.5%, and/or triglycerides ≥5.65 mmol/L, was comprised of seven patients who were enrolled and treated at the primary study site that captured baseline leptin levels.

Eight (89%) of the nine GL patients and all seven patients in the PL subgroup were female in Study FHA101. Most patients in both groups were ≥18 years of age at the time of enrolment, including 6 of 9 GL patients and all seven patients in the PL subgroup; median ages were 25.0 and 42.0 years, respectively. Median leptin level was 0.7 ng/mL for GL patients with data available and 7.0 ng/mL in the PL subgroup.

7.2.1 Efficacy Results

The major metabolic abnormalities associated with LD include hypertriglyceridemia, severe insulin resistance and/or diabetes and/or hepatic steatosis/steatohepatitis, often associated with elevated liver enzymes and hepatomegaly. Results presented in this section are focused on the co-primary efficacy endpoints of HbA1c and serum triglycerides.

7.2.1.1 Study NIH 991265/20010769

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

Both males and females with GL sustained clinically meaningful and statistically significant reductions in HbA1c and triglycerides at Month 12/LOCF.

For patients in the PL subgroup, treatment with metreleptin also led to clinically meaningful and statistically significant reductions in HbA1c with a mean change of -0.9% ($p<0.001$). However, due to an extreme outlying result for 1 patient as explained below, results for triglycerides in the overall PL subgroup showed a small mean percent increase between baseline and Month 12/LOCF for the full analysis set. The outlying result was observed in a patient who had a >1000% increase in triglycerides to the primary endpoint; the only patient in the study with this level of change at Month 12. This patient was terminated from the study by the Investigator two days prior to the Month 12 assessment for noncompliance with study drug administration. When the data for this noncompliant patient are excluded from analysis, the results for mean percent change from baseline to Month 12/LOCF in triglycerides for the PL subgroup showed a clinically meaningful and statistically significant change of -37.4% ($p<0.001$), which was consistent with the results observed for the GL group.

7.2.1.2 Study FHA101

In general, the efficacy results in the supportive Study FHA101 were consistent with those reported for Study NIH 991265/20010769, although the number of patients included in analyses for this study was small.

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

7.2.2 Safety Results

The pivotal study was not placebo-controlled, and the lack of a placebo control limits interpretation of the safety data of metreleptin, which is particularly relevant in this patient population that often has multiple serious co-morbidities as part of their underlying disease. These co-morbidities may be expected to progress over the course of a study spanning several years. This is further confounded by the relatively small patient numbers and the relative lack of published data on the natural history of the condition.

Thus, prospective observation of metreleptin treated patients in this registry will continue evaluation of the safety of metreleptin.

Across the two studies supporting the Marketing Authorization Application, a total of 148 patients with GL and PL received metreleptin during clinical trials. Safety and efficacy data were analyzed in a subgroup of partial LD patients with the following characteristics: 12 years of age and above with leptin levels <12 ng/mL, TG ≥ 5.65 mmol/l and/or HbA1c ≥ 8%. Overall

metreleptin has a favorable profile and the most frequent adverse reactions reported in the Summary of Product Characteristics are summarized in Table 1.

Table 1: Adverse Reactions Reported with Metreleptin in > 1 Patient During Clinical Studies in Generalized and the subgroup of Partial LD patients and Post-marketing Experience.

System Organ Class	Very common	Common	Frequency not known[a]
Infections and infestations			Influenza, Pneumonia
Immune system disorders			Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycemia	Decreased appetite	Diabetes mellitus, Hyperphagia, Insulin resistance
Nervous system disorders		Headache	
Cardiac disorders			Tachycardia
Vascular disorders			Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders			Cough, Dyspnea Pleural effusion
Gastrointestinal disorders		Abdominal pain, Nausea	Abdominal pain upper, Diarrhea, Pancreatitis, Vomiting
Skin and subcutaneous tissue disorders		Alopecia	Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders			Arthralgia, Myalgia
Reproductive system and breast disorders		Menorrhagia	
General disorders and administration site conditions		Fatigue, Injection site bruising, Injection site erythema, Injection site reaction	Fat tissue increased, Injection site hemorrhage, Injection site pain, Injection site pruritus, Injection site swelling, Malaise, Peripheral swelling
Investigations	Weight decreased	Neutralizing antibodies	Blood glucose abnormal, Blood triglycerides increased, Drug specific antibody present, Glycosylated hemoglobin increased, Weight increased

a. Global post marketing experience

7.2.2.1 Additional Information is Provided for the Following Safety Concerns

Hypersensitivity (anaphylaxis, urticarial, and generalized rash)

There have been reports of generalized hypersensitivity (e.g. anaphylaxis, urticaria or generalized rash) in patients using metreleptin. Anaphylactic reactions may follow immediately after administration of the medicine. If an anaphylactic reaction or other serious allergic reaction occurs, administration should be permanently discontinued immediately and appropriate therapy initiated.

Acute pancreatitis associated with discontinuation of metreleptin

Non-compliance with, or abrupt discontinuation of, metreleptin may result in worsening hypertriglyceridemia and associated pancreatitis, particularly in patients with risk factors for pancreatitis (e.g. history of pancreatitis, severe hypertriglyceridemia). If a patient develops pancreatitis whilst being treated with metreleptin, it is advised that metreleptin be continued uninterrupted, as stopping treatment abruptly may exacerbate the condition. If metreleptin must be stopped for any reason, tapering of the dose over a two-week period is recommended in conjunction with a low-fat diet. During tapering, monitor triglyceride levels and consider initiating or adjusting the dose of lipid-lowering medicinal products as needed. Signs and/or symptoms consistent with pancreatitis should prompt an appropriate clinical evaluation.

Hypoglycemia with concomitant use of insulin and other anti-diabetics

There is a risk of hypoglycemia in patients treated with metreleptin 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 two weeks of treatment. Once insulin requirements have stabilized, dose adjustments of other anti-diabetics may also be needed in some patients to minimize the risk of hypoglycemia.

Closely monitor blood glucose in patients on concomitant insulin therapy, especially those on high doses, or insulin secretagogues and combination treatment. Patients and carers should be advised to be aware of the signs and symptoms of hypoglycemia.

In clinical studies, hypoglycemia has been managed with food/drink intake and by modifying the dose of anti-diabetic medicinal product. In case of hypoglycemic 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. Rotation of injection sites is recommended in patients co-administering insulin (or other subcutaneous medicinal products) and metreleptin.

Medication errors

Patient may be either under or overdosed as a result of the medication error.

Treatment with metreleptin should be initiated and monitored by a healthcare provider (HCP) experienced in the diagnosis and management of metabolic disorders. In addition, there are instructions related to the method of administration and dosing, overdose, and information

regarding shelf life, storage, handling and disposal. In addition, the 30-vial package is designed as a compact carton containing 30 vials which is equivalent to a month's supply.

The 3 mg and 5.8 mg vials address the concern of medication errors in patients who require a lower maximum daily dose (injection volume).

Lymphoma

Cases of lymphoma (two cases of peripheral T-cell lymphoma and one case of anaplastic large-cell lymphoma) have been reported while using metreleptin in clinical studies. Acquired LDs are associated with autoimmune disorders that are associated with an increased risk of lymphomas. A causal relationship between the medicinal product treatment and the development and/or progression of lymphoma has not been established. The benefits and risks of treatment should be carefully considered in patients with acquired generalized LD and/or in patients with significant hematological abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy).

Serious and severe infections secondary to ADAs with blocking activity

Serious and severe infections can be debilitating for patients and require intensive medical support. In patients with serious and severe infections, continuation of metreleptin should be at the discretion of the prescriber and consideration should be given by the prescriber to have these patients tested for the presence of ADAs with blocking activity. To facilitate this testing, prescribers who report spontaneous events of serious and severe infections, through the safety reporting pathway will be contacted and invited to consider testing for their patients. Assimilation of blocking activity data in patients with severe and/or serious infections, and the provision of test results back to treating HCPs, together with annual analysis and aggregate reporting in periodic benefit-risk evaluation reports will help understand the risk. An association between the development of a blocking activity against metreleptin and serious and severe infections cannot be excluded.

Unplanned pregnancy

Metreleptin may increase fertility, due to restoration of LH release. Unplanned pregnancy may have significant medical and social implications for the patient.

Loss of efficacy, potentially due to ADAs with blocking activity

In clinical studies, ADAs to metreleptin occurred very commonly (88%) in patients. A blocking activity of the reaction between metreleptin and a recombinant leptin receptor was observed in vitro in the blood of majority of patients (96%) but the impact on the efficacy of metreleptin could not be clearly established. An association between the development of ADAs with blocking activity and serious and severe infections cannot be excluded and continuation of metreleptin should be at the discretion of the prescriber as well as having these patients tested for the presence of ADAs with blocking activity.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

The MEASuRE registry will add to the knowledge about metreleptin gained from clinical trials by providing information on long-term safety and effectiveness in patients treated with metreleptin in routine clinical practice. It will provide the opportunity to obtain further data on the incidence rates of specific safety events and on areas of missing information. The MEASuRE Registry is a post marketing requirement / specific obligation following approval by the FDA as PMR 2456-1 and with the EMA as SOB001.

8.2 OBJECTIVES

8.2.1 Primary Objectives

To determine the incidence and severity of the following safety events in patients treated with metreleptin as part of standard clinical practice:

- Acute pancreatitis associated with the discontinuation of metreleptin, and all cases of fatal or necrotizing pancreatitis
- Hepatic adverse events
- Hypoglycemia stratified by severity and concomitant antidiabetics dose modifications
  - Severe hypoglycemia is defined as any blood glucose level below 40 mg/dL. (2.2 mmol/L)
- Hypersensitivity reactions
- Serious and severe infections, including serious infections resulting in hospitalization and death
  - Severe infections are defined as any infection that requires IV antibiotic, antifungal or antiviral; or leads to radiologic, endoscopic, or operative interventions (Consistent with CTCAE version 5.0)
  - Please refer to Section 11.1 for a definition of serious adverse event
- Loss of efficacy, potentially due to ADAs with blocking activity
- In addition to clinical suspicion of loss of efficacy, patients should be tested for neutralizing antibodies in cases of any significant increases in HbA1c, serum triglycerides or an increase of patient's insulin requirements that might suggest loss of efficacy and could not be explained otherwise (please refer to Section 9.2.7 for further information on the assessment of immunogenicity in conjunction with suspected loss of efficacy).
- New diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis)
- Exacerbation of existing autoimmune disorders
- All cancers (excluding non-melanoma skin cancer) by cancer type

- Exposed pregnancies and pregnancy outcomes stratified by planned or unplanned
- All-cause deaths (including causes of death)
- Medication errors

8.2.2 Secondary Objectives

- To describe the overall demographic and clinical characteristics, and metreleptin exposure in all patients treated with metreleptin (pattern of use analysis)
- To describe routine laboratory measurements that could be inferred as effectiveness endpoints (including HbA1c, FPG and TG) over time

8.2.3 Exploratory Objectives

The registry will provide the opportunity to obtain further data on:

- Use in pregnancy and lactation
- Use in elderly
- Effect of metreleptin on brain development
- Effect of metreleptin on bone metabolism
- Effect of metreleptin on sexual maturation (Tanner staging)
- Neuroendocrine parameters and levels of the following hormones: testosterone, estradiol, LH, FSH and free T3 and T4
- Contingent on study sample size, the study will also estimate the incidence rate of the primary outcomes of interest by patient characteristics
- In patients with results from immunogenicity testing, the incidence of ADAs with blocking activity will be estimated

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, multicenter, prospective, observational, voluntary study of patients treated with metreleptin therapy as part of standard clinical practice in the US and EEA.

In the US, metreleptin is approved for the treatment of generalized lipodystrophy (GL). In the EEA metreleptin is approved for the treatment of both GL and partial lipodystrophy (PL).

In the US, the study will attempt to enroll at least 100 patients treated with metreleptin. Patients will be enrolled from US and EEA to achieve this target. All patients enrolled from the US will be followed for a minimum of ten years unless they withdraw consent to participate in the registry or die.

In the EEA, the registry will offer enrolment to all patients treated with metreleptin. Patients will be followed for the duration of the lifecycle of the product unless they withdraw consent

to participate in the registry or die. In the EEA, a disease registry, the European Registry for Lipodystrophy (ECLip), already exists and follows all patients with lipodystrophy irrespective of the treatments prescribed. Patients in the EEA who are enrolled in ECLip and are prescribed metreleptin will be encouraged to enroll in MEASuRE.

The registry is non-interventional; all treatment decisions, including visit frequency, are made at the discretion of the patient's HCP, and are not mandated by the study design or protocol. All eligible patients, at sites where prescribers are participating investigators, who have taken at least one dose of metreleptin will be approached to participate, irrespective of whether they are taking metreleptin at the time of enrolment. Every effort will be made to enroll as many prescribers and their eligible patients as possible.

The target study population will include patients who have taken at least one dose of commercial metreleptin. Consecutive patients within each participating prescriber's practice initiating treatment with metreleptin and who meet the enrolment criteria will be invited and encouraged to consent and enroll into the registry and will be followed per the protocol. Inclusion criteria are broad and exclusion criteria are limited so as to include a representative population of patients taking metreleptin as per usual clinical practice.

In the US, the Risk Evaluation and Mitigation Strategy (REMS) Program limits the use of metreleptin only to patients with GL. Physicians who treat patients for conditions other than GL can enroll these patients in the registry provided they are not receiving treatment as part of a clinical study. In the view of the Sponsor, most US patients enrolled in the registry will be GL patients, as only those patients are eligible to be prescribed metreleptin. However, the protocol does not exclude others who might be treated with metreleptin through commercial supply.

In the EEA, metreleptin is approved for use in GL and PL and so it is anticipated that both GL and PL patients will be enrolled in the registry.

9.1.1 Primary Endpoints

The primary endpoints are the occurrence of acute pancreatitis associated with the discontinuation of metreleptin, all cases of fatal or necrotizing pancreatitis, hepatic adverse events, - hypoglycemia stratified by severity and concomitant antidiabetics dose modifications, hypersensitivity reactions, serious and severe infections (including serious infections resulting in hospitalization and death), loss of efficacy (potentially due to ADAs with blocking activity), new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), exacerbation of existing autoimmune disorders, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes stratified by planned or unplanned, all deaths (including causes of death) in patients treated with metreleptin and medication errors.

Details on the above objectives and the strategy used for their identification are reported in the Endpoint Adjudication Committee (EAC) Charter.

9.1.2 Secondary Endpoints

The secondary endpoints include demographics, clinical characteristics, metreleptin exposure and routine laboratory measurements in all patients treated with metreleptin.

9.1.3 Exploratory Endpoints

Data on the use of metreleptin in pregnancy and lactation, its effect on brain development, bone metabolism and sexual maturation in children, and its effect in the elderly, will be collected. In addition, levels of the following hormones (neuroendocrine parameters): testosterone, estradiol, LH, FSH and free T3 and T4, will be the only parameters collected if available. Contingent on study sample size, the study will also estimate the incidence rate of the primary outcomes of interest by patient characteristics. In patients with results from immunogenicity testing, the incidence of ADAs with blocking activity will be estimated.

9.1.4 Sample Size / Power

For the US, the goal of the registry is to enroll at least 100 patients initiating treatment with metreleptin. The sample size calculation is based on patient recruitment experience in the clinical development program and published prevalence information, it is estimated that 20 patients per year will enroll in the registry. Assuming an annual lost to follow-up rate of 10%, the cumulative person-time information during the study period is 656 person-years. Given this expected number of person-years of exposure, the study would provide 95% assurance for the detection of at least one occurrence of a given, relatively rare major safety event with an incidence rate of approximately ½ of one percent (approximately 0.46%), that is, an event that would occur approximately once in every 220 person-years of exposure. This calculation assumes independence of person-years. In addition, this sample size, on a per-person basis, would provide two-sided 95% confidence limits with a maximum width of approximately ±8.8% for events that have a per-person incidence of 30% or less.

In the EEA, patients will be enrolled indefinitely for the duration of the lifecycle of the product, and as such, no power calculation was performed.

9.2 SETTING

9.2.1 Study Population

All patients treated with metreleptin through commercial supply and enrolled in the registry will be categorized into one of two patient cohorts: metreleptin new user cohort or metreleptin prevalent user cohort.

- Metreleptin new user cohort includes patients who are initiating treatment with metreleptin through commercial supply at the time of providing written consent for registry enrolment.

- Metreleptin prevalent (prevalent current and prevalent prior) user cohort includes patients who are treated with metreleptin through commercial supply but before registry enrolment and/or patients treated with metreleptin through commercial supply but coming off metreleptin treatment from a non-commercial source (e.g., clinical studies). For definition of prevalent current and prevalent prior users refer to Section 9.7.1.

9.2.2 Patient Consent

At the time of registry enrolment, written consent is required for all study patients as per local requirements.

- Patients who have the ability to understand the requirements of the registry and provide written informed consent for themselves.
- Patients of any age who are unable to respond on their own behalf whose parent or guardian has the ability to understand the requirements of the registry and provide written informed consent. Pediatric patients will also be included in all discussions, as appropriate based on age, in order to obtain written assent.

  In cases where a written informed consent cannot be obtained at the study site, informed consent can be obtained remotely. For remote consent, a copy of the Informed Consent Document will be mailed to the patient's address, along with a return envelope. The patient is asked to review the consent form in its entirety. The patient can discuss their decision to participate with friends and family before returning the signed form. The patient will be encouraged to discuss any questions they may have with their study physician. The physician should sign and date the consent form after the completed consent form has been received from the patient. If the patient agrees to participate, a signed and dated copy of the consent form signed by both parties, will be provided for their records.

9.2.3 Inclusion Criteria

Patients who are treated with metreleptin as part of clinical care i.e., those:

- who provide written consent before enrolment into registry, and
- are treated with metreleptin through commercial supply at the time or before enrolment into registry, or
- are coming off the metreleptin clinical studies and continuing or restarting treatment with metreleptin through commercial supplies.

Please refer to Appendix 1 (Section 13.1) for specific details relating to patient eligibility in Germany.

9.2.4 Exclusion Criteria

Patients currently treated with an investigational agent as part of a clinical trial.

9.2.5 Prescribing Physician Enrolment

In the US, metreleptin is dispensed through a limited number of specialty pharmacies. Prescriber information (geographic location, specialty and medical degree) and patient

demographic characteristics will be collected at the specialty pharmacies. Prescriber information provided by the specialty pharmacies will be used to identify physicians who have prescribed metreleptin and invite them to participate in the registry.

Information from the specialty pharmacies will also be used to identify the number of patients for whom each prescriber has written a metreleptin prescription. Each prescribing physician participating in the registry will be asked to invite all of his/her eligible patients to participate in the registry, with a goal of capturing the majority of patients treated with metreleptin.

In the EEA, patients will be enrolled in MEASuRE through the ECLip Registry. The ECLip board will be notified of the countries where metreleptin has achieved reimbursement. For each country where reimbursement is achieved and metreleptin is available commercially, all physicians in that country who are enrolled in ECLip will be invited to participate in the registry for any patients that they prescribe metreleptin. If reimbursement is achieved in a country and the physicians are not enrolled in ECLip, they will be encouraged to enroll in ECLip so that their patients can be enrolled in the registry. Every effort will be used to encourage prescribers to enroll in the registry and to enroll all their eligible patients for whom metreleptin is prescribed so that a heterogeneous sample of practice sites can be included. Patient recruitment will be monitored in an ongoing manner, with specific reviews during the interim analyses.

For the US and EEA, all participating physicians will be trained on the study protocol.

9.2.6 Patient Enrolment and Retention to Minimize Number of Patients Lost to Follow-up

The target study population will include all eligible patients who will take at least one dose of commercial metreleptin. The prescribing physician participating in the registry at each associated healthcare facility will be asked to keep a list of all patients who are treated with metreleptin. The list will be used to track the status of patient recruitment and enrolment as well as to further inform the progress of registry enrolment. All eligible patients treated with metreleptin at active sites will be informed of this registry and will be asked to participate and sign an Informed Consent Form. The reason prescribers decline to participate in the registry will be captured.

All patients will be followed for at least 10 years in the US or for the duration of the product lifecycle in the EEA, unless the patient withdraws consent or dies. Upon enrolment, a registry kit including site materials, patient enrolment materials and patient retention materials will be provided to all enrolled patients who provide a written consent. The site materials and the patient enrolment materials will help to inform patients on the purpose and the added scientific value of their participation in the registry. The patient retention materials including the starter pack (study guide and appointment reminder) and direct mailers will keep patients informed on the study progress/updates and facilitate interest in continuous participation in the registry during the follow-up period.

Site will be trained on the importance of patient retention and the strategies to follow up with the patients that do not attend the visits. If a patient does not return to the site within 12 consecutive months since his/her last visit, the treating physicians (or designee) will attempt to call the patient and document the patient's reason for not returning. After not returning to the sites for more than 12 consecutive months, sites will attempt to contact patients at various times of the day and evening, and on different days of the week. Patients who do not return for scheduled visits and cannot be contacted after at least four attempts over a four-week period will be considered lost to follow-up.

If the patient cannot be contacted after the due diligence process, the treating physicians and their site staff will attempt to contact the patient's designated secondary contacts, including the patient's primary care physician after the final attempt before determining the given patient as lost to follow-up. The following information will be collected from these sources and will be recorded on the appropriate case report form (CRF or eCRF [electronic case report form]):

- Patient vital status
- Change in patient contact information
- Change in patient's health status
- Reasons why the patient was lost to follow-up

If the patient's care is transferred to another HCP, the treating physician (or designee) at the site where the patient has been enrolled will be responsible for obtaining the required follow-up information from the new treating physician, unless the new treating physician agrees to participate directly in the registry.

If the patient's vital status remains unknown, the Study Coordinating Centre may seek to obtain the patient's vital status through any National Death Registry and, if the patient is deceased, the date and cause of death.

9.2.7 Immunogenicity Assessment

Patients with suspected loss of metreleptin efficacy (e.g., worsening glycemic control, increases in triglycerides) or loss of endogenous leptin activity (e.g., severe infections) should be tested for ADAs with *in-vitro* blocking activity.

Blocking activity will be assessed via the Global Immunogenicity Program, if consent is given through this program which provides testing for antibodies against metreleptin and human endogenous leptin free of charge.

If a patient is positive for ADA, they will be asked to submit follow-up samples until ADA are no longer detected or until notified. Participation is voluntary. Additional data may be collected in the Global Immunogenicity Program to follow the clinical profile of the patient in correlation to antibody levels. Data available from this program may be included in MEASuRE for patients enrolled in both programs.

9.3 VARIABLES

Available data will be collected prior to starting commercial metreleptin and from all standard care visits after starting commercial metreleptin. In the US data will be collected for at least 10 years following enrolment into the registry unless the patient dies or withdraws consent. In the EEA, enrolment will continue for the lifecycle of the product following enrolment into the registry unless the patient dies or withdraws consent. Event specific information will be structured for statistical analysis as described below. Independent variables are those that describe the treatment exposure of primary interest. Dependent variables are those that describe the outcomes of interest. Covariates are additional variables that may predict the outcome of interest.

9.3.1 Outcomes/Primary Endpoint Variables

Occurrence of acute pancreatitis associated with discontinuation of metreleptin, all cases of fatal or necrotizing pancreatitis, hepatic adverse events, hypoglycemia stratified by severity and concomitant antidiabetics dose modifications, hypersensitivity reactions, serious and severe infections (including serious infections resulting in hospitalization and death), loss of efficacy, potentially due to ADAs with blocking activity, new diagnoses of autoimmune disorders, exacerbation of existing autoimmune disorders, all cancers, exposed pregnancies and outcomes stratified by planned or unplanned, all-cause deaths and medication errors are the outcomes of interest and thus the dependent variables for purposes of statistical analysis.

9.3.2 Exposure/Independent Variables of Interest

Metreleptin exposure, which is the independent variable for analysis purposes, will be quantified in terms of duration of treatment.

Length of exposure to the treatment will be defined as (the last treatment date – first treatment date). The frequency of the length of exposure will be presented in six-month duration categories during the entire study period. In the US, the minimum duration of follow up is defined as 10 years. In the EEA, the duration of follow up is defined as the duration of the lifecycle of the product.

For patients who start, stop and resume metreleptin treatment, the interruption in treatment will not be subtracted from the duration of exposure. If patients experience an event during the period of treatment interruption, it is not possible to rule out an association with previous metreleptin exposure. Therefore, periods of interruption will be counted as part of the total duration of metreleptin exposure. For patients who stop metreleptin treatment and do not resume during the duration of this study, the study will continue to monitor these patients for occurrence of primary outcomes if feasible. Therefore, the information on restarting the therapy can be collected if it occurs. Duration of observation will be defined as (the last clinical follow up visit date - first treatment date).

9.3.3 Metreleptin Exposure Information

Information will be collected primarily from physician prescription information recorded in the patient's medical record. In the US, if this information is not available, metreleptin prescription data will be obtained from specialty pharmacy shipments and/or dispensing record information if available.

9.3.4 Other Covariates/Control Variables

Patient characteristics and clinical covariates include demographics, past medical and pregnancy history, lipodystrophy diagnosis (including subtypes), and medication use including previous metreleptin exposure. Clinical characteristics include vital signs and relevant laboratory test results over time (e.g., height / weight / blood pressure, HbA1c, plasma glucose concentration, triglycerides, HDL-C [high density lipoprotein-cholesterol], LDL-C [low density lipoprotein-cholesterol], total cholesterol, ALT [alanine aminotransferase], AST [aspartate aminotransferase], ALP (alkaline phosphatase), PT (prothrombin time), total bilirubin, creatinine, estimated glomerular filtration rate [eGFR], urine protein to creatinine ratio, leptin levels). Past medical history includes comorbidities of interest such as diabetes, pancreatitis, hepatic steatosis and steatohepatitis, hepatic cirrhosis, proteinuric nephropathies, sepsis, serious infection, microvascular and macrovascular complications. Concomitant medications used for the management of lipodystrophy and metabolic abnormalities (dose, frequency, length of therapy) will be described. In patients with immunogenicity testing result, any evidence of ADAs with blocking activity will be documented. Healthcare utilization in the prior six months is defined as the number of clinic/hospital/emergency room (ER) visits.

Table 2: Demographic, Clinical and Medication Covariates

Variable	Categories
Demography	
Date of birth/ year of birth (EEA)	Date
Gender	Categorical
Race/ethnicity	Categorical
Pregnancy status	Categorical
Development milestones and Tanner staging in children	Categorical
Lipodystrophy diagnosis (including subtypes)	Categorical
Date of diagnosis	Date
Basis of diagnosis	Categorical
Vital signs and relevant clinical and laboratory test results	
Height/weight/blood pressure	Continuous
DEXA Bone Scan	Continuous
Routine laboratory Measurements:	
HbA1c, plasma glucose concentration	Continuous
Lipid profile (triglycerides, HDL-C, LDL-C, total cholesterol)	Continuous
Liver function (e.g. ALT, AST, ALP and PT)	Continuous
Total bilirubin	Continuous
Renal function (e.g. proteinuria, blood urea nitrogen)	Continuous
Result of immunogenicity testing	Continuous
Leptin levels	Continuous
Neuroendocrine parameters, testosterone, estradiol, LH, FSH and free T3 and T4	Continuous
Procedures/Results of diagnostic tests	Categorical
Comorbidities of interest including	
Diabetes	Categorical
Pancreatitis	Categorical
Hepatis steatosis and steatohepatitis and hepatic cirrhosis	Categorical
Proteinuric nephropathies	Categorical
Sepsis	Categorical
Serious infection	Categorical
Microvascular and macrovascular complications	Categorical

Variable	Categories
Medications used for the management of lipodystrophy and metabolic abnormalities	Categorical
Dose	Continuous
Frequency	Continuous
Length of therapy	Continuous
First treatment date	Continuous
Last treatment date	Continuous
Metreleptin treatment	Categorical
Dose	Continuous
Frequency	Continuous
Length of therapy	Continuous
First treatment date	Continuous
Last treatment date	Continuous
ADAs and blocking activity status	Categorical
Patient vital status, if deceased, date and cause of death	Categorical
Healthcare utilization between study visits-number of clinic/hospital/ER visits	Continuous

9.4 DATA SOURCES

9.4.1 Study Data Acquisition

At each specified bi-annual data collection time point, clinical information will be abstracted from all patient visits including scheduled and/or unscheduled visits since the last data collection time point. Data will be abstracted from patient medical records and charts and will be entered by the treating physicians or their site staff at centers into a computerized data system using structured eCRFs. In the US, if a study center is unable to enter the data electronically, paper forms will be used and submitted to the Study Coordinating Centre and the Coordinating Centre will assist with electronic data entry at a later date. This process is described in the Data Management Plan. The data to be collected at enrolment (including baseline data points) and follow-up data collection points are described below. In Europe, if data are entered on a paper form, the data entry will be managed through the ECLip Study Coordinating Centre.

9.4.1.1 Baseline and Enrolment Data

Baseline data will be collected for all patients to be able to assess the treatment effect of metreleptin. Baseline data are defined as the latest available data prior to initiating metreleptin use (i.e. metreleptin naïve data).

The following data points constitute baseline and will be collected at the enrolment visit:

- Vital signs and relevant clinical and laboratory test results (e.g., height, weight, calculated body mass index, blood pressure, HbA1c, FPG, TGs, HDL-C, LDL-C, total cholesterol, ALT, AST, ALP, PT, total bilirubin, creatinine, neuroendocrine parameters, testosterone, estradiol, LH, FSH and free T3 and T4, eGFR, urine protein to creatinine ratio, baseline leptin level, DEXA bone scan), development milestones in children and Tanner staging.
- Concomitant Medications used for the management of lipodystrophy and metabolic abnormalities (dose, frequency, ongoing status), at the time of initiation of metreleptin therapy.

The following data are collected at the enrolment visit for all patients:

- Characteristics of patients treated with metreleptin, including demographics, health behaviors (tobacco and alcohol exposure), pregnancy status and pregnancy history, family history, lipodystrophy diagnosis (including subtypes), past medical history.
- Comorbidities of interest including diabetes, pancreatitis, hepatic steatosis, steatohepatitis, cirrhosis, proteinuric nephropathies, sepsis, serious infection, microvascular and macrovascular complications.
- For any patient previously treated with metreleptin through a clinical trial, the date that metreleptin was initiated in the clinical trial will be collected.
- Metreleptin treatment: first treatment date, dose, frequency, length of therapy.
- Healthcare resource utilization: the number of in-patient and ER visits, as well as clinic and out-patient visits to be collected since starting metreleptin.

Exception:

For prevalent metreleptin users ONLY: The following data are entered into the EDC at the relevant Data Collection Points from the time of initiation of commercial metreleptin:

- Vital signs, relevant clinical and laboratory test results (e.g., height, weight, calculated body mass index, blood pressure, HbA1c, FPG, TGs, HDL-C, LDL-C, total cholesterol, ALT, AST, ALP, PT, total bilirubin, creatinine, neuroendocrine parameters, testosterone, estradiol, LH, FSH and free T3 and T4, eGFR, urine protein to creatinine ratio, baseline leptin level, DEXA bone scan), development milestones in children and Tanner staging.
- Concomitant Medications used for the management of lipodystrophy and metabolic abnormalities (dose, frequency, length of therapy, first treatment date, last treatment date), results of ADA and blocking activity status.

9.4.1.2 Follow-Up Data

The time period for follow up data refers to the period following the date the patient started receiving commercial metreleptin. For prevalent users, this requires retrospective data collection to the time of the initiation of commercial metreleptin.

Vital signs and relevant laboratory test results and relevant procedures and diagnostic tests will be captured during subsequent routine clinical visit if these tests are performed as part of usual care. Data collection will occur in association with the routine clinical practice and entered ideally on at least a bi-annual basis, noting the timing as associated with the most recent clinical visits. The duration of follow up is defined as 10 years after the last patient enrolment date for the US and for the EEA as the duration of the life-cycle of the product. The following data will be collected from medical records at the data collection time points, as available:

- Adverse events (event, start and stop dates, severity, outcome, relationship to metreleptin) including non-serious adverse events and serious adverse events
- Developmental milestone and Tanner staging in children / adolescents
- Vital signs and relevant routine laboratory test results
- Height / weight / blood pressure
- HbA1c, fasting plasma glucose concentration
- Lipid profile (TG, HDL-C, LDL-C, total cholesterol)
- Liver profile (e.g., ALT, AST, ALP, PT)
- Total bilirubin (direct and indirect if captured as part of normal clinical practice)
- Renal function (e.g., creatinine, eGFR) and proteinuria (urine protein to creatinine ratio)
- Leptin levels
- Neuroendocrine parameters, testosterone, estradiol, LH, FSH and free T3 and T4
- DEXA scan
- Immunogenicity testing if performed (antibodies to metreleptin, blocking activity to metreleptin in antibody positive samples)
- Procedures/other diagnostic tests
- Changes in metreleptin treatment
  - Dose
  - Frequency
  - Treatment change dates
- Changes in concomitant medications used for the management of metabolic abnormalities (diabetes, hypertriglyceridemia), blood pressure, and other complications of lipodystrophy
  - Dose
  - Frequency
  - Treatment change dates
- Number of clinic/hospital/ER visits between study visits
- Pregnancy (if applicable)

  - Current pregnancy history
  - Pregnancy outcome
- Neonatal characteristics
- Congenital anomalies
- Pediatric follow-up at three months
- Any abnormalities identified since birth

Patients with evidence of blocking activity at any time point, will be encouraged to participate in the Global Immunogenicity Program and additional data will be collected via this program, if consent is given.

In patients who discontinue metreleptin therapy, additional follow up data collection will continue, if feasible.

9.4.1.3 Pregnancy and Pregnancy Outcomes

Data on female patients who become pregnant during metreleptin therapy or within six months of stopping therapy will be collected throughout pregnancy until outcome.

The primary outcomes of interest are major congenital abnormalities. Also reported will be pregnancy outcomes, such as therapeutic or elective abortion and fetal loss. Pregnancy losses and birth defects will be classified as consistent with that used in the Metropolitan Atlanta Congenital Defects Program (MACDP) (Correa-Villaseñor, 2003) (National Center for Birth Defects and Developmental Disabilities, 2004). All birth outcomes will be evaluated based on earliest exposure to metreleptin.

Pregnancy outcomes will be classified into one of the following mutually exclusive categories: spontaneous abortion/miscarriage; elective abortion; fetal death/stillbirth; or live birth. Other pregnancy outcomes of interest are: ectopic pregnancy; maternal death; and neonatal death.

Among live births, the information on birth weight, gestational age, multiple births, congenital anomalies, and nature and age at diagnosis of any pediatric abnormalities will be collected at three months pediatric follow-up in addition to the information collected for pregnancy and outcomes.

Table 3: Timetable of Assessments

Assessment	Enrollment	All Standard Care Visits Following Enrollment [a]	Withdrawal [b]	Ad-hoc Assessment (at Onset of Specific Safety Event)
Informed Consent	●			
Demography -Date of birth/ year of birth (EEA) -Gender -Race/ethnicity	●			
Medical and pregnancy history	●			
Development milestones and Tanner staging in children	●[c]	●	●	●
Lipodystrophy diagnosis (including subtypes) -Date of diagnosis -Basis of diagnosis -Additional diagnosis information	●	●		
Vital signs and relevant clinical and laboratory test results over time -Height / weight / blood pressure -HbA1c, FPG -Lipid profile (TG, HDL-C, LDL-C, Total cholesterol) -Liver profile (e.g., ALT, AST, ALP, PT) -Total bilirubin -Renal function (e.g., creatinine, eGFR) and proteinuria (urine protein to creatinine ratio) -Leptin levels -Neuroendocrine parameters, testosterone, estradiol, LH, FSH and free T3 and T4 -DEXA scan	●[d]	●	●	●
Pregnancy status [e]	●	●	●	●

Assessment	Enrollment	All Standard Care Visits Following Enrollment [a]	Withdrawal [b]	Ad-hoc Assessment (at Onset of Specific Safety Event)
Procedures/Results of diagnostic tests	●	●	●	●
Comorbidities of interest including: -Diabetes -Pancreatitis -Hepatic steatosis and steatohepatitis, and hepatic cirrhosis -Proteinuric nephropathies -Sepsis -Serious infection -Microvascular and macrovascular complications	●	●	●	●
Primary endpoints and all adverse events	●	●	●	●
Concomitant medications used for the management of lipodystrophy and metabolic abnormalities (dose, frequency, length of therapy) -Drug class -Dose -Frequency -Length of therapy -First treatment date -Last treatment date	●[f]	●	●	●
Metreleptin treatment -First treatment date -Dose -Frequency -Length of therapy -Current therapy (during follow up visit) -Treatment stop date	●	●	●	●

Assessment	Enrollment	All Standard Care Visits Following Enrollment [a]	Withdrawal [b]	Ad-hoc Assessment (at Onset of Specific Safety Event)
-Reason for treatment stop/interruption -Treatment restart date				
Results of antibody testing -Suspect of potential loss of efficacy	●	●	●	●
Healthcare resource use -Hospitalization -Clinic visits -Emergency room visits	●	●	●	●
Patient Vital Status[g]; If deceased, date and cause of death	●	●	●	●

[a] Data collection as per current practice, visits that fall closest to time points described above.

[b] Withdrawal data are captured at the last data collection point and end of study form in the MEASuRE database.

[c] For prevalent users, development milestones and Tanner staging will be collected at enrolment and baseline timepoints.

[d] For prevalent users, vital signs and lab results will be collected at enrolment and baseline timepoints.

[e] Data on female patients who become pregnant during metreleptin therapy or within six months of stopping therapy will be collected throughout pregnancy until outcome.

[f] For prevalent users, concomitant medications will be collected at enrolment and baseline timepoints. At baseline, length of therapy, first treatment date and last treatment date are not required.

[g] Follow up with patient, patient's secondary contacts, with support from the CRO (contract research organization)/ designee. Additionally, search may include data of any National Death Registry, or other public records.

9.4.2 Steering Committee

A Steering Committee will be established and will include clinicians and scientists with expertise in the areas of lipodystrophy and metabolic disease, epidemiology, endocrinology, hepatology as well as a biostatistician. Committee members will provide subject matter expertise for the program. The Steering Committee will be responsible for reviewing the data from the registry over time and comparing it to the product information.

Based on their review the Steering Committee will make recommendations to the Sponsor regarding its conduct, as well as assist in study execution and interpretation and in publication planning and manuscript review.

9.4.3 Endpoint Adjudication Process

An endpoint adjudication (EA) process will be established to review, evaluate and validate specific safety concerns identified in the study. The EA process will require all Investigators to make an initial safety event designation. Subsequently, the Investigator's safety event designation will be reviewed and adjudicated by three independent physicians with the appropriate medical background and expertise - two physicians to each adjudicate events within their specialty and a third physician to further evaluate and make the final determination for any discrepancies identified between the two.

9.5 STUDY SIZE

The goal of the registry is to enroll all patients treated with commercially available metreleptin. In the US, the goal of the registry is to enroll at least 100 patients. In the EEA, the study will enroll for the duration of the product lifecycle. Every effort will be made to enroll patients at the time of initiating therapy or continuing therapy upon/after the commercial availability of metreleptin.

9.6 DATA MANAGEMENT

9.6.1 Data Collection

The data collection time point is on at least a bi-annual basis, (twice a year) starting with the baseline and enrolment visit at the time of registry enrolment and continuing throughout the entire follow-up period, including retrospective data collection to the time commercial metreleptin was initiated.

Data collection is primarily based on the data extraction of medical records from all standard care visits including scheduled and/or unscheduled throughout the entire follow-up period.

9.7 DATA ANALYSIS

All the planned analyses below will be performed in two separate cohorts: metreleptin new user cohort vs. metreleptin prevalent user cohort. All analyses will be stratified by metreleptin new users and metreleptin prevalent users defined upon study enrolment to address potential

immortal-time bias associated with prevalence patients. The potential for a pooled, stratified analysis using both cohorts will be evaluated through the use of propensity score methods, using the covariates outlined in Section 9.3.4. Analyses of GL and PL cohorts will be performed if the enrolled numbers permit these analyses. In addition, analyses of Pediatric cohorts and further sub-group analyses may be performed.

The Sponsor may integrate the MEASuRE data with relevant data collected in other metreleptin studies to further enhance the Sponsor's knowledge on the effect of metreleptin in lipodystrophy patients for scientific purposes.

9.7.1 Data Analysis for New and Prevalent Users

The registry will include patients who are initiating metreleptin therapy at the time of enrolling into the registry (new users), as well as prevalent users. This latter group of patients may have been exposed to metreleptin through participation in a clinical trial or an expanded access program or may have initiated commercial metreleptin treatment prior to registry enrolment. Including patients who participated in clinical trials or an expanded access program will allow continued long-term assessment of patients beyond clinical trial participation. In addition, patients who were exposed to metreleptin treatment, but discontinued treatment will also be encouraged to enroll. It is recognized that patients who initiate metreleptin after it is commercially available but discontinue shortly thereafter may not be inclined to enroll in the registry since they are no longer on product. These patients could differ in demographic characteristics from those who enroll and may also have a different safety profile if they discontinued treatment due to an adverse event. Thus, efforts will be made to enroll these patients as well. It is also recognized that there may be an off-treatment timeframe between the first treatment with metreleptin, either in the clinical or in the commercial setting, and the patient enrolment and treatment in the registry. For the prevalent metreleptin users, data collection will include information on any SAEs experienced during the six months prior to registry enrolment . For any SAEs experienced outside this window in prevalent metreleptin users (> 6 months prior to enrolment in MEASuRE), events should be reported in the MEASuRE database under Medical History.

All primary analyses will be performed separately by "metreleptin new user cohort" vs "metreleptin prevalent user cohort". Analyses will also be performed for the combined cohorts, based on the propensity score stratification.

If 10% or more of total patients have used metreleptin in the past but are no longer using it for at least 120 days prior to study enrollment, the prevalent user cohort may be further stratified into two cohorts:

- Prevalent current user cohort: patients who at the time of registry enrollment are currently treated (within the last 119 days) with metreleptin through commercial supply or who are continuing with metreleptin treatment through commercial supply after coming off a metreleptin clinical study.

- Prevalent prior user cohort: patients who at the time of registry enrollment were previously treated with metreleptin through commercial supply but whose most recent treatment was at least 120 days or more prior to registry enrollment or who continued with metreleptin treatment through commercial supply after coming off a metreleptin clinical study but terminated metreleptin treatment at least 120 days prior to enrollment.
- Note the data will be presented by Metreleptin new user cohort and Metreleptin prevalent user cohort by default. Only if more than 10% of patients qualify for the Prevalent prior user cohort, the output will include this third cohort.

Analyses will be based on baseline (pre-metreleptin) data. Incidence of specific safety concerns and other adverse events will be annualized to account for exposure time.

9.7.2 Statistical Analysis Methods

The primary objective of this study is to estimate the incidence of primary outcomes of interest in the patients treated with metreleptin. A confidence interval (CI) approach is chosen for the rate of the events of interest.

The details of analyses for each of the primary and secondary objectives and other aspects of analyses and statistical assumptions and approaches (e.g., missing data, analysis window) will be included in the statistical analysis plan (SAP).

The primary population for analysis will consist of all patients who have received at least one dose of metreleptin, regardless of the indication for which the treatment is received.

Data will be analyzed by subgroups; metreleptin new user cohort, metreleptin prevalent user cohort; by indication, GL and PL and if required by region, US and EEA. In addition, analyses of Pediatric cohorts and further sub-group analyses may be performed.

9.7.3 Analysis Plan for Primary Objectives

Crude event rates and incidence rates of primary outcomes of interest and their associated 95% CIs will be estimated for the overall patient population treated with metreleptin. Major safety events as listed in Section 8.2.1 will be analyzed separately; in addition, the rates of any event, of specific subtypes within categories (for example, deaths by cause of mortality as well as all deaths, different causes for hospitalization, type of autoimmune disorder) and of combined groupings of similar events (for example, newly diagnosed plus exacerbated autoimmune disease, etc.) will be presented. Analysis will also be performed for other event categories, such as any serious event, and events resulting in metreleptin discontinuation, and others to be defined in the statistical analysis plan. Event rates will be estimated by dividing the number of patients with specific safety concerns by the accumulated number of treated patients; for this analysis, a specific event will be counted only once per patient. Incidence rates will be estimated by dividing the number of patients with specific safety concerns by the accumulated person-years at risk. For this analysis, the person-years at risk for those with the event is

cumulative up to the time of the event; for those without the event, the person-years at risk represents all available exposure time. In addition, Kaplan-Meier method will be used to estimate incidence rate and account for censored data; this analysis will use cumulative person-years as the time variable.

In patients with subsequent episodes during the study window, both the total number of events and incidence of repeat occurrence will be estimated.

9.7.4 Analysis Plan for Secondary Objectives

Demographic and clinical characteristics of all metreleptin treated patients will be described.

Drug exposure will be summarized, including total duration, frequency of dose interruptions, discontinuations and dose reductions, and duration of dose interruptions and reductions, as appropriate.

Within each patient, results of laboratory measurements at his/her standard care visits will be described and compared to values at baseline. The standard care visits will be scheduled per clinical practice and will be recorded and tracked in the electronic data capture (EDC) to confirm timing vs data collection time points. The number of patients without available laboratory measurements at each data collection time point will be documented.

9.7.5 Analysis Plan for Pregnancy and Pregnancy Outcomes

All pregnancy outcomes will be described in detail and the statistical analysis will be considered as described below if >10 live births reported at least 1 birth defect per live birth.

If and when >10 live births reported at least 1 birth defect per live birth:

- The total prevalence of birth defects is calculated by dividing the number of cases with birth defects by the total number of live births.
- Live birth prevalence, fetal death prevalence, and Prevalence of Termination of pregnancy for fetal anomaly following prenatal diagnosis will be calculated using the same methodology described by EUROCAT to allow comparison with the European Surveillance of Congenital Anomalies that uses this convention (http://eurocat-network.eu/accessprevalencedata/prevalencetables, http://www.eurocat-network.eu/newprevdata/Calculations%20of%Prevalence%20and%20CIs.pdf)
- The analysis of birth defect outcomes will be stratified by earliest trimester of exposure, maternal age, and other maternal risk factors, as appropriate. Statistical analysis will consider maternal age as it influences the rate of chromosomal abnormalities.

9.7.6 Analysis Plan for Immunogenicity

Assessment of immunogenicity is described in the Global Immunogenicity Program. All analysis and reporting will be performed under that Program and will utilize demographic and clinical data obtained from this registry for patients enrolled in both programs, when possible. Immunogenicity testing results performed under the Metreleptin Immunogenicity Program will

be shared with the investigator and included in registry database for patients participating in both programs. In patients with results from immunogenicity testing, the incidence of blocking activity will be summarized.

9.7.7 Data Analysis Time Window

Data will be analyzed according to the following timeframe:

Per Periodic Safety Update Report timelines according to the European Union reference dates list.

Per specific safety concerns at the level of the case via the adjudication committee.

Annually in aggregate.

9.7.8 Censoring Criteria

If a patient does not return to the site for any of his/her scheduled standard care visits over a period of 12 consecutive months or more since their last visit, the patient will be censored and determined as at risk for lost to follow-up.

If and when there is a patient(s) who is determined as at risk for lost-to-follow-up based on the study definition, various attempts will be made to contact patients to obtain the information described in Table 3 as withdrawal assessment. Data collected at the last biannual planned data collection time point containing the patient's last visit prior to the patient's lost to follow-up will be included in all formal analyses.

9.7.9 Handling Missing Data

There is a potential for missing data. Missing observations will not be imputed in the analysis of individual items.

9.8 QUALITY CONTROL

The data obtained from patients will be checked for accuracy prior to inclusion in the MEASuRE Registry. Due to the nature of this program, sites will be monitored through routine calls and other types of correspondence. Monitoring of data will be primarily managed centrally by the study data management team with specific criteria that may trigger on site monitoring. All inbound and outbound calls from sites related to monitoring will be tracked, including inquiry type, center ID and resolution.

9.8.1 Site Training and Initiation

The site start-up meeting will be held to train the treating physicians and their site staff on the study requirements and use of the EDC system for study data entry by the CRO management personnel. The CRO management personnel will contact each site to initiate and review the site initiation procedures.

9.8.2 Site Monitoring and Data Collection

Ongoing site management will occur throughout the entire duration of the study on each bi-annual data collection time point and on an as-needed basis according to the Site Monitoring Plan to ensure the treating physicians and their site staff reporting and recording data from all standard of care visits including scheduled as well as unscheduled into the EDC system.

Sites are requested to complete data entry in a timely manner following patient visits. Sites who do not complete data entry for more than two consecutive, confirmed, patient visits will be considered non-compliant. The CRO management personnel will contact the non-compliant sites to explore reasons for non-compliance in data entry. Remote re-training/reviewing study data entry and collection procedures will be considered and determined on an as-needed basis.

9.8.3 Database Retention and Archiving of Study Documents

The prescribing physicians participating in this registry study must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The prescribing physicians participating in this registry study must contact the Sponsor prior to destroying any records associated with the study. Location of the database and supporting documentation will be outlined in the final observational study report.

9.8.4 Registration of Study on Public Website

This study has been registered on https://ClinicalTrials.gov (NCT02325674). This study will be entered into the HMA-EMA Catalogue of Real-World Data studies.

9.9 LIMITATION OF THE RESEARCH METHODS

This registry represents the largest effort to-date to study rates of specific safety concerns in patients treated with commercially available metreleptin in the US and EEA. The study will observe a larger number of patients than was studied in the metreleptin clinical development program and will enable more precise estimation of the incidence of the primary endpoints. The intended enrolment of all indicated patients receiving metreleptin whether or not they are currently taking metreleptin will attempt to minimize the potential impact of sampling bias on estimation of these major safety events in patients with this rare disease. As therapy will not be withheld to allow time for a site to be activated patients are allowed to enter the registry after they have initiated therapy with commercial metreleptin, with available data entered retrospectively. Thus, there is the potential of survivor bias. To address this limitation, an exploratory analysis will be performed to compare safety information in patients who initiated metreleptin prior to enrolment to those who initiated commercial metreleptin at the time of enrolment into the registry.

Specifically, comparability of demographic and baseline characteristics will be evaluated, as well as potential differences in incidence of specific safety events. In addition, a propensity score adjustment method will be used, in order to evaluate the incidence of specific safety

concerns in a balanced stratification using, e.g., quintiles of propensity scores. Complete details of this method will be provided in the SAP.

The nature of observational registries based on standard clinical care and optional participation by physicians and patients introduces sources of potential bias. The precision of estimated incidence of specific safety concerns rates will be impacted by the accuracy with which these events are diagnosed and noted in the medical record, the number of follow-up visits captured per patient, and the number of patients enrolled in the registry. The generalizability of findings will be determined by how well the patients in the registry represent the population of patients treated with metreleptin. Interpretation of findings will need to occur in the context of these and other potential biases inherent in this type of observational research.

9.10 OTHER ASPECTS

The study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (ISPE, 2008) and applicable regulatory requirements and with the ethical principles originating from the World Medical Association Declaration of Helsinki (World Medical Association, 2013).

10 PROTECTION OF HUMAN SUBJECTS

10.1 ETHICS COMMITTEE REVIEW AND INFORMED CONSENT

This study may require review and approval by ethics committees and / or informed consent as per local requirements.

The prescribing physicians participating in this registry must ensure that the required approvals from Ethics Committees, Independent Review Committees, Regulatory Authorities, and/or other local governance bodies are obtained before study initiation at the site.

In accordance with local regulations, patients will be required to provide written consent before enrolment into the study, prescribing physicians participating in the registry study must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are clearly and fully informed about the purpose of the study, potential risks, and the patient's rights and responsibilities when participating in this study.

In case where a written informed consent cannot be obtained at the study site, please refer to Section 9.2.2.

10.2 CONFIDENTIALITY OF STUDY DATA

The Sponsor plans to use data collected for the MEASuRE study for future research in pseudonymized form. As indicated in Section 9.7, the MEASuRE data may be integrated with other metreleptin studies. The Sponsor will assign designated personnel within the organization to manage the archives. Access to these archives will be restricted to those individuals. Any

requests for access to unpublished data will be evaluated by the Sponsor and the Steering Committee, where applicable on a case-by-case basis.

The confidentiality of records that could identify patients within the database will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

In order to ensure patient confidentiality, patients will be assigned a unique identifying number. The key matching identification numbers with patient names will be maintained by the site, and only the unique identifier will be recorded on the data collection forms with the patient initials. Upon enrolment, in localities where this is permissible, patients will be required to provide their name, phone and electronic mail (e-mail) contact information and similar information on secondary contacts. This information will not be entered into the study clinical database. The treating physician and their site staff will securely store this information separately from other study information. This information will only be used to obtain patient vital status and disposition if the patient becomes lost to follow-up. To ensure compliance with regulatory requirements and to support potential future analysis, data will be retained for 10 years after the Metreleptin marketing authorization expires.

In any presentations or publications of the results of the study, the patients' identities will remain anonymous and confidential. the Sponsor, its designee(s), and various government health agencies may inspect the records of the study. Every effort will be made to keep the patients' personal medical data confidential.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 ADVERSE EVENT DEFINITION

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The causal relationship to metreleptin is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between metreleptin and the AE.
- Not related: There is not a reasonable causal relationship between metreleptin and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

An **Adverse drug reaction (ADR)** is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (related). Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Medical conditions that exist before the beginning of the study are not considered as an ADR in the study, unless the condition worsens after starting metreleptin.

A **non-serious adverse event** is an AE not classified as serious.

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

1. results in death
2. is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3. requires inpatient hospitalization or causes prolongation of existing hospitalization (See note below)
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly/birth defect
6. is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.).

Suspected transmission of an infectious agent, pathogenic or non-pathogenic, via metreleptin is an SAE.

An **overdose** is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events are handled as SAEs.

NOTE:

The following hospitalizations are not considered SAEs in this study:

- A visit to the emergency room or other hospital department of <24 hours that does not result in admission (unless considered an important medical or life-threatening event).
- Elective surgery planned prior to signing consent.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons).

Immunogenicity: in accordance with Section 9.2.7, events of severe/serious infection or lack of efficacy can trigger the collection of additional immunogenicity data, through the dedicated Global Immunogenicity Program. In addition to the investigators reporting the ADA results in the EDC, ADA results will also be received by the Sponsor, who will capture them in the safety database.

In addition to the above definitions, reports of breastfeeding, use in paediatric or elderly populations, abuse, off-label use, misuse, medication error, occupational exposure and lack of therapeutic efficacy are also collected even if not associated with AEs, serious or non-serious. These are classified as special situation reports.

11.2 EVENTS OF SPECIAL INTEREST (ESI)

Subset of adverse events that are of particular interest due to their potential impact on patient safety. These events are predefined based on the pharmacological properties of the product, preclinical data, known effects of related drugs, or emerging data from ongoing trials.

For this study, the following events (regardless of relatedness to the treatment), will be considered as ESI:

- All-Cause Deaths
- Acute pancreatitis associated with the discontinuation of metreleptin
- Fatal or necrotizing pancreatitis
- Hepatic Adverse Events
- Hypoglycemia

- Hypersensitivity reactions
- Serious and severe infections
- Serious infections resulting in hospitalization or death
- Loss of efficacy
- New diagnoses of autoimmune disorders
- Exacerbation of existing autoimmune disorders
- Cancers (excluding non-melanoma skin cancer)
- Exposed pregnancies and pregnancy outcome
- Medication errors

A detailed list of the Medical Dictionary of Regulatory Activities (MedDRA) strategy for their reporting is included in EAC Charter.

11.3 ADVERSE EVENT COLLECTION AND REPORTING

Following the patient's written consent to participate in the study, non-serious AEs, SAEs, Events of Special Interest (ESI) /Adverse Events of Special Interest (AESI) special situation reports and specific safety concerns, collectively known as safety information, whether or not related to metreleptin, as well as, pregnancies, AEs associated with maternal exposure, and pregnancy outcomes ascertained in the study, must be reported individually in the time frames noted below. All AEs collected will also be reported in aggregate in the final study report. If only limited information is initially available, follow-up reports may be required.

The collected safety information should be as complete as possible. The initial safety report should at least refer to the following minimum information, then followed up to obtain a complete safety report:

- An identifiable healthcare professional reporter (the reporter can be identified by either name or initials, or address or qualification, e.g., physician, dentist, pharmacist, nurse).
- An identifiable patient (at least one among patient initials, patient number, date of birth/year of birth (EEA) or age or age group, gestation period, gender).
- At least one suspected active substance/medicinal product.
- At least one suspected adverse reaction.

All events should be followed until resolution or stabilization and follow-up may continue after the end of the study, if appropriate.

11.3.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all safety information, whether or not related to the metreleptin, must be collected, including those thought to be associated with protocol-specified procedures. All safety information, i.e. AEs, SAEs, ESIs/AESIs, special situation reports and specific safety concerns, will be captured in the EDC system by the sites within 24 hours/1 business day of awareness to comply with regulatory requirements. Although overdose and cancer are not always serious by regulatory definition, these events should also be captured in the EDC within 24 hours/1 business day of awareness. Alternatively, in case of any access issues to the EDC, sites may email the sponsor/CRO to report the SAE.

If only limited information is initially available, follow-up reports may be required.

11.3.2 Procedure for Reporting Pregnancy

Pregnancy information is collected regardless of seriousness or if an AE is associated with it. Pregnancies should be reported through the EDC system within 24 hours/1 business day of awareness.

The same timelines apply when pregnancy outcome information is available.

If it is discovered a patient is pregnant or may have been pregnant at the time of exposure to metreleptin, the pregnancy, AEs associated with maternal exposure and pregnancy outcomes must be captured in the EDC system within 24 hours/1 business day of awareness. If only limited information is initially available, follow-up reports may be required. As part of Pharmacovigilance monitoring, follow-up information will be solicited at each trimester and at the delivery of the child. Follow-up information should be obtained on pregnancy outcomes for one year following the birth of the offspring.

11.3.3 Procedure for Reporting Overdose

Overdose information is collected regardless of seriousness and even if no SAE is associated with the event.

Overdoses should be reported through the EDC system within 24 hours/1 business day of awareness.

11.3.4 Non-Serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of the study. Non-serious AE information should also be collected from the start of the observational period intended to establish a baseline status for the subjects.

Non-serious adverse events must also be captured in the EDC system within 24 hours/1 business day of awareness to comply with regulatory requirements.

Non-serious AEs should be followed to resolution or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of metreleptin under study and for those present at the end of the study, as appropriate.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim study reports will be submitted to the FDA and EMA on an annual basis. In the US, a final study report will be submitted upon completion of the study (i.e., when the 100th patient reaches 10 years of follow-up). In the EEA, the annual reports will continue during the lifecycle of the product.

13 REFERENCES

Chan, J. L. and Oral, E. A. (2010). "Clinical classification and treatment of congenital and acquired lipodystrophy." Endocr Pract 16(2): 310-323.

Chiquette, E., Oral, E. A., Garg, A., Araújo-Vilar, D. and Dhankhar, P. (2017). "Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges." Diabetes Metab Syndr Obes 10: 375-383.

Correa-Villaseñor, A., Cragan, J., Kucik, J., O'Leary, L., Siffel, C. and Williams, L. (2003). "The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention." Birth Defects Res A Clin Mol Teratol 67(9): 617-624.

Garg, A. (2004). "Acquired and inherited lipodystrophies." N Engl J Med 350(12): 1220-1234.

ISPE (2008). "Guidelines for good pharmacoepidemiology practices (GPP)." Pharmacoepidemiol Drug Saf 17(2): 200-208.

MYALEPT® USPI (2014). Myalept US Prescribing Information DAC, A. P.

World Medical Association (2013). "Declaration of Helsinki: ethical principles for medical research involving human subjects." Jama 310(20): 2191-2194.

13.1 APPENDIX 1: ELIGIBILITY CRITERIA FOR GERMANY

In Germany the "MEASuRE" study is categorized as a standalone study, and it will comply with the specifications of the German Medicinal Products Act.

Specifically, for conduct as a prospective, non-interventional study in Germany, all eligible patients will be treated in line with the approved EU SmPC; no patients treated off-label will be included or followed-up within the study.

13.2 APPENDIX 2: PRIOR AMENDMENTS AND SUMMARY OF CHANGES

The Protocol Amendment Summary of Changes Table for the current amendment is located in Section 5.

Below are summaries of prior amendment(s) by region in reverse chronological order for each.

AEGR-734-403 (SOB001; EU MEASURE)				
Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
1	29Jan2019	N/A	Initial protocol	N/A
2	05Jul2019	Table 2, Sections: 8.2.1, 9.1.3, 9.2.6, 9.7.5	Update	Response to request from CHMP.
N/A	01Feb2021	Protocol	Retired	Merging protocol AEGR-734-403 with the US Protocol AEGR-734-400 for the purpose of creating the Global MEASuRE protocol under AEGR-734-400. There will be no more activities under this protocol number.

AEGR-734-400 (V 1 – V 6: US MEASURE; FROM V 7: GLOBAL MEASURE)				
Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
1	15 Jan 2014	N/A	Initial (Not Implemented)	N/A
2	10 Dec 2014	Appendix A	Update (Not Implemented) Also referred to as Revision 1.	To include Appendix A: Outcome Definition and Validation, in response to the FDA's comment.
3	06 Feb 2015	Section 7.6.2	Update (Not Implemented) Also referred to as Revision 2.	The marketing authorization holder has been changed from Amylin to Aegerion and the author has been updated.

AEGR-734-400 (V 1 – V 6: US MEASURE; FROM V 7: GLOBAL MEASURE)				
Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
				Clarification of patient's vital status.
3	04 May 2015	Protocol Title; Section 2.2 & 7.1 Study Design; Section 7.2.1 Study Population; 7.2.7 Immunogenicity Section; Table 3; Section–9.2.2 Procedure for Reporting Pregnancy; Appendix A	Update (Not Implemented) In error, this version was referred to as V 3.0.	Protocol Title was updated. Enrolment duration statement was clarified. Metreleptin cohorts were defined. Basis of Diagnosis and Procedures/Results of Diagnostic Tests added. Pregnancy statement clarified. Appendix A has been removed from this document and will be a standalone document referred to as the endpoint adjudication committee (EAC) charter.
4	22 Oct 2015	Section 7.2.1 Study Population; Section 7.2.4 Exclusion Criteria; Appendix A	Update (First Implemented)	Metreleptin cohorts definitions updated. Clarified statement about the Expanded Access Patients. Appendix A which had been part of the FDA-accepted version of the protocol (i.e., version dated 06 Feb 2015, accepted by FDA on 22 Feb 2015) has been reintroduced and replaces references to the Endpoint Adjudication Committee charter.

AEGR-734-400 (V 1 – V 6: US MEASuRE; FROM V 7: GLOBAL MEASuRE)				
Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
5	04 Jan 2017	Section 7.4.3	Update (Not Implemented)	Section 7.4.3 was updated in an effort to streamline the endpoint adjudication process and enhance identification of ESIs per protocol commitments.
6	11 May 2017	Administrative changes; Study Roles; Section 7.4.3	Update (Implemented)	The role of Medical Director and Medical Monitor was combined. Section 7.4.3 was updated in an effort to streamline the endpoint adjudication process.
7	01 Feb 2021	N/A	Update – submitted to FDA Incorporates approved EU protocol v2 (AEGR-734-403) to create the harmonized global MEASuRE protocol as notified to the EMA via the Annual re-assessment	Changes due to creating the Global MEASuRE protocol (refer to regional Summary of Changes for further details). Changes include, but are not limited to: Change in Sponsor from Aegerion to Amryt. Change in references from EU to EEA due to Brexit. Addition of wording on how patients from EEA and the US will be enrolled in the global registry. Removal of the 45-day window around the biannual data collection timepoints to encourage continuous data entry and reduce missing data.

AEGR-734-400 (V 1 – V 6: US MEASURE; FROM V 7: GLOBAL MEASURE)				
Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
				Revision of text on the monitoring of the data entered by the site. Addition of further wording on the immunogenicity follow-up program.
V7.1 – FDA V8.0 in EEA	19 July 2021	Section 6, Section 8.2.1, Section 9.4.1, Section 9.6.1, Section 9.7.1 and Table 3, Section 9.8.2	Update following comments from FDA– submitted to FDA. Minor amendment in EEA. Not submitted to EMA. Submitted to country level Regulatory Authorities	Updated EEA milestone to Q4 2021. Change in text to collect data on all cases of fatal or necrotizing pancreatitis. Change in definition of baseline data collection from ‘before the start of commercial metreleptin’ to ‘before the start of metreleptin therapy’. Clarity provided for data collection time period, to explicitly state data collected from start of commercial metreleptin use, in line with Section 9.4.1.2 Change in focus for non-compliance from patient visit to data entry. This is more representative of an observational registry as there is flexibility in patient visits per standard of care. Minor administrative changes elsewhere.

AEGR-734-400 (V 1 – V 6: US MEASURE; FROM V 7: GLOBAL MEASURE)				
Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
8.1	20 Oct 2021	Section 4, Section 5, Section 8.2.1, Section 9.1.1 and Section 9.3.1	Update – submitted to FDA as v7.2 following comments on 7.1. then finalized as v8.1 in line with EEA protocol. Minor amendment in EEA. Not submitted to EMA. Not submitted to country level Regulatory Authorities.	Primary objective relating to infection has been updated to explicitly state that serious infections resulting in hospitalization and death will be collected separately to data on serious and severe infections.
8.2	14 Dec 2021	Section 1, Section 9.2.3, Appendix 1	Non substantial amendment in US. No submission to FDA planned. Submission planned to IRBs. Non substantial amendment in EEA. No submission to EMA planned. Submissions to country level Regulatory Authorities and ECs planned.	Appendix 1 relating specifically to eligibility criteria in Germany has been added to the protocol. Other administrative changes elsewhere.
8.3	10 Apr 2025	Cover Page, Synopsis/Registry Information,	Update submitted to FDA.	Medical Contact, Author and Sponsor Signatory name updated due to changes in personnel.

AEGR-734-400 (V 1 – V 6: US MEASURE; FROM V 7: GLOBAL MEASURE)				
Number	**Date**	**Section of Study Protocol**	**Amendment or Update**	**Reason**
		Sponsor's Approval, MAH Holder and Section 9.7.	Non substantial amendment in EEA. No submission to EMA planned.	MAH updated to Chiesi due to acquisition. Confidentiality statement updated accordingly. Section 9.7 updated to allow for analyses of Paediatric cohorts and further sub-group analyses to enhance our knowledge on the effect of metreleptin in lipodystrophy patients for scientific purposes.