Statistical Analysis Plan

PROTOCOL AEGR-734-401 (V4.0, 08FEB2018)

A 36-MONTH, MULTICENTER, OPEN LABEL PHASE 4 STUDY TO EVALUATE THE IMMUNOGENICITY OF DAILY SC METRELEPTIN TREATMENT IN PATIENTS WITH GENERALIZED LIPODYSTROPHY

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan (V2.1, 13MAR2024) for Protocol AEGR-734-401 (V4.0, 08FEB2018).

The SAP signature page applies to both SAP text and SAP Templates (outputs shells or Tables/Listings/Figures (TLFs) shells). Templates must be sent to the customer with the first draft SAP text.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	02AUG2019	Tracy Franklin	Not Applicable – First version
2.0	09FEB2024	Tracy Franklin, Tingxuan Li, Imaani Easthausen, Leonor Rodrigues	• Study Objectives: Added exploratory objectives • Planned Analyses: Added discussion of dry run • Analysis Sets: o Added clarification that EAS varies by both measure of interest and timepoint o Clairfied that EAS will be used in primary and effectiveness analyses • General Considerations: o Updated software versions o Added discussion of when partial date imputations are applicable • Output Presentations: Added discussion of additional data visualizations to be generated as needed and/or appropriate • Dispositions and Withdrawals: o Added analyses for patients receiving at least one dose of Metreleptin, patients valid for the

			EAS, and total study participation in years • Demographic and Other Baseline Characteristics: Added derivation for age at informed consent • Medical History: o Updated definition of medical history to align with the CRF. o Added derivation for age at lipodystrophy diagnosis • Study Medicaiton Exposure: Updated derivation for duration of exposure accounting for interruptions • Primary Immunogenicity Analysis: o Added analysis set for the primary analysis o Added descriptions of the primary analyses to be performed o Added all relevant derivations for primary analyses • Exploratory Analyses: Added fasting plasma glucose and leptin/metreleptin concentration as exploratory variables • Safety Outcomes: o Added definitions of AESIs o Added logic for selection of events to include in AE tables stratified by immunogenicity variables • Updated data windowing conventions • Updated partial date conventions

			• Overall improvement of document structure, language and consistency
2.1	13MAR2024	Imaani Easthausen, Leonor Rodrigues	• Windowing conventions updated. There was an issue with some of the scheduled days. Now all of them are calculated as follows: floor (Study Month Number * 30.4).

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1. ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomic therapeutic class
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
DILI	Drug induced liver injury
EAS	Effectiveness analysis set
ECLIA	Electrochemiluminescence immunoassay
FAS	Full analysis set
HbA1c	Hemoglobin A1c
HuL	Human leptin
MEASuRE	Metreletpin Effectiveness and Safety Registry
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimum required dilution
NAb	Neutralizing antibodies
PT	Preferred term
RB	Receptor blocking
RWES	Real-world evidence solutions
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment emergent adverse event
TLFs	Tables, listings and figures
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of the effectiveness and safety data for Protocol AEGR-734-401: A 36-Month, Multicenter, Open Label Phase 4 Study to Evaluate the Immunogenicity of Daily Subcutaneous (SC) Metreleptin Treatment in Patients with Generalized Lipodystrophy. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on the protocol number AEGR-734-401 V4.0, dated 08FEB2018 and case report forms (CRFs) V7.0, dated 28MAY2021. If there are differences between the statistical methods documented in the protocol and this document, the methods in this document will supersede what is in the protocol. Any changes from the planned analyses of the final SAP will be documented in the case study report.

3. STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective is to evaluate the immunogenicity associated with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy.

3.2 Secondary Objectives

The secondary objective is to assess 2 methods of measuring *in vitro* neutralizing activity to metreleptin.

3.3 Safety Objectives

The safety objectives are:

- To evaluate the safety and tolerability in relation to the development of or absence of anti-metreleptin or anti-human leptin (HuL) antibodies, and/or *in vitro* neutralizing activity to metreleptin in patients with congenital or acquired generalized lipodystrophy.
- To measure *in vitro* neutralizing activity in all patients with suspected loss of response (worsening of metabolic control) or endogenous leptin action (severe infections or sepsis) at time of adverse event report.

3.4 Exploratory Objective

The exploratory objective is to evaluate the efficacy achieved with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy.

4. STUDY DESIGN

4.1 General Description

This study is an open-label, Phase 4 trial to provide an assessment of the immunogenicity associated with metreleptin and of any major potential risks due to development of antibodies to metreleptin. The study is being conducted to comply with an Food and Drug Administration post-marketing requirement.

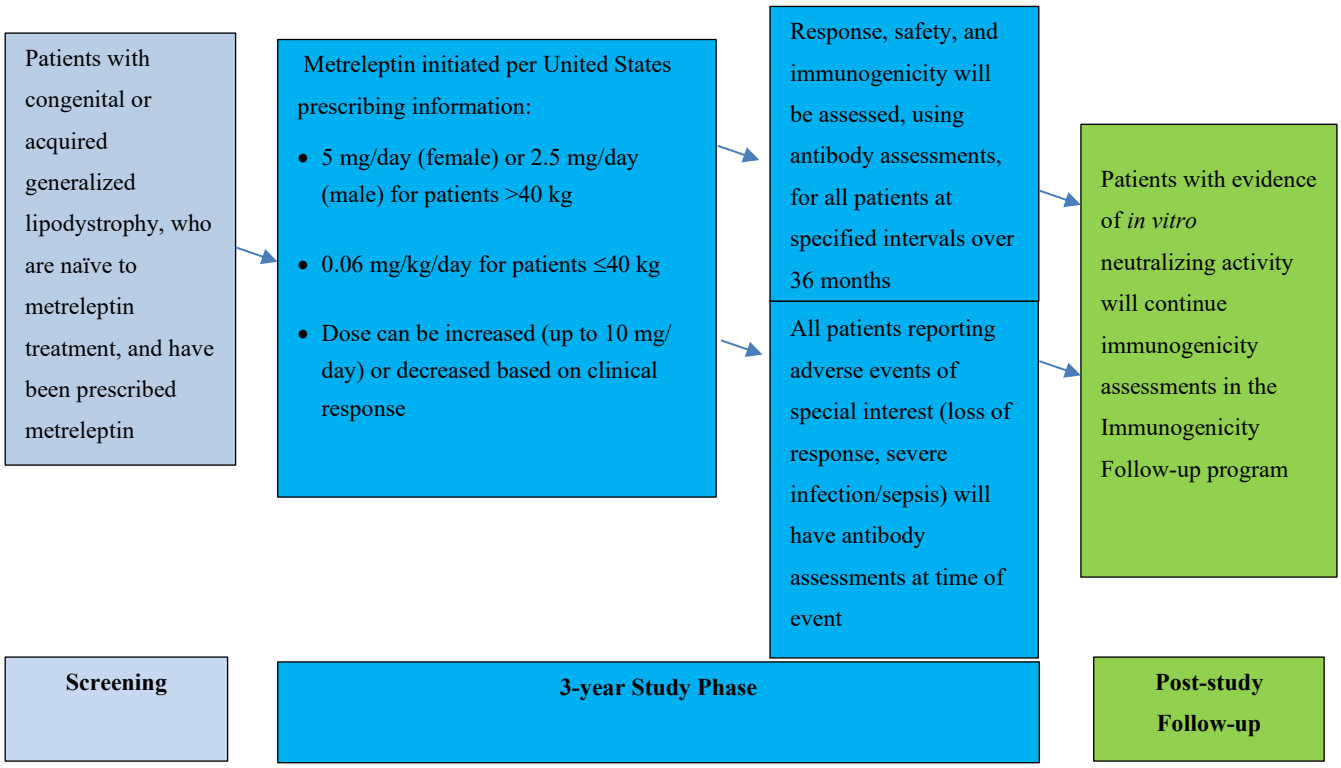
Patients who have been prescribed metreleptin for generalized lipodystrophy, who meet all enrollment criteria and who have signed informed consent for this study at Screening (Visit 1) will receive the first dose of metreleptin at Enrollment/Baseline (Visit 2) at the study site. Patients will return to the study site for follow-up and collection of blood samples at regular intervals (at Month 1, 2, 4, 6, 9, 12, 18, 24, 30, and 36), for a total of 12 visits over approximately 3 years (36 months). Eleven patients who have been prescribed metreleptin will be enrolled.

All patients, including those with suspected loss of metreleptin efficacy (worsening of metabolic control) or endogenous leptin action (serious or severe infections or sepsis) should be tested for *in vitro* neutralizing activity.

The study flow diagram is presented in **Figure 1**.

Patients who sign informed consent and meet all inclusion/exclusion criteria will be enrolled in the study. Assessments will be made at the times specified in the Study Plan (**Table 1** of protocol). At the end of the 3-year study period, patients who still have *in vitro* neutralizing activity should enroll in the separate Immunogenicity Follow-up Program for continued immunogenicity monitoring.

Figure 1: Study Schematic



4.2 Schedule of Events

The schedule of events can be found in **Table 1** of the protocol.

4.3 Changes to Analysis from Protocol

There are no changes to the analysis from the protocol.

5. PLANNED ANALYSES

The following analyses are planned for this study: 1) Final Analysis to be completed after database lock with 2) a dry run to be completed prior to database lock. The purpose of the dry run is to generate all analyses prior to database lock to ensure the planned analyses as described are appropriate. The dry run will use real study data. The results will not be shared with study sites. Any changes to the planned analyses based on the dry run will be documented in this SAP for

transparency. Given the key study endpoints are objective measures, the risk of bias as a result of the dry run is minimal.

5.1 Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Real-World Evidence Solutions (RWES) Biostatistics following Sponsor Authorization of this SAP, Database Lock, and Sponsor Authorization of Analysis Sets.

6. ANALYSIS SETS

6.1 Full Analysis Set (FAS)

The full analysis set (FAS) will contain all enrolled subjects.

6.2 Safety Analysis Set (SAF)

The safety analysis set (SAF) will contain all enrolled subjects who receive at least one documented dose of metreleptin and will be used in the assessment of safety.

6.3 Effectiveness Analysis Set (EAS)

The effectiveness analysis set (EAS) will contain all enrolled subjects who received at least one documented dose of metreleptin and who have baseline and post-dose laboratory results on the measure of interest at the time point of interest. By definition, the EAS will vary by both measure and timepoint. The effectiveness analysis sets will be used in the primary and exploratory analyses.

7. GENERAL CONSIDERATIONS

7.1 Baseline

The Enrollment/Baseline Visit (Visit 2) is the baseline visit, and will be conducted within 28 days of the Screening Visit. First dose of metreleptin will be administered at Baseline after all procedures for the Screening Visit, specified in **Table 1** of the protocol, are conducted.

7.2 Software Version

All analyses and datasets will be programmed using Statistical Analysis Software Version 9.4 or higher. R Version 4.1.3 or higher may be used to generate data visualizations as needed.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Summaries, Tests and Confidence Intervals

There will be no hypothesis testing. All data will be summarized by descriptive statistics and/or listings. Number of patients with missing data will be reported where applicable. Continuous variables will be summarized by mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages of each category. Missing values will be excluded from percentage calculations. Where appropriate, two-sided, 90% and 80% Clopper-Pearson exact confidence intervals (CIs) will be included as well.

8.2 Missing data

Generally, missing data will not be imputed. As applicable, partial dates may be imputed for the purposes of categorizing medications as prior/concomitant and defining treatment emergent adverse events (TEAEs). Partial date handling is described in **Appendix 1**. Imputed dates will NOT be presented in listings. Where applicable, counts of missing observations will be reported.

9. OUTPUT PRESENTATIONS

The shell document provided with this SAP describes the presentations for this study and therefore the format and content of the summary tables, listings and figures (TLFs) to be provided by IQVIA RWES Biostatistics.

In addition to the below described analyses, other data visualizations may be generated as needed to further evaluate variables and endpoints of interest. All additional data visualizations generated will be included in the TLFs.

10. DISPOSITION AND DISCONTINUATIONS

Subject disposition and discontinuations will be presented for all enrolled patients (FAS). The following will be summarized: patients screened (FAS), patients receiving at least one dose of Metreleptin (SAF), patients valid for the EAS, patients completing the study, discontinuations, reasons for discontinuation, and total study participation in years. See **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported.

10.1 Derivations

- Study participation duration (years) = [(end of study date – informed consent date + 1)/365.25].

11. DEMOGRAPHIC AND OTHER CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the SAF. The following demographic and other baseline characteristics will be reported for this study. See **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported.

- Age at informed consent (years)
- Sex
- Ethnicity
- Race
- Participation in Metreleptin Effectiveness and Safety Registry (MEASuRE)

Note: MEASuRE a sister study by the same Sponsor designed to evaluate the long-term safety and effectiveness of metreleptin under normal conditions of clinical practice.

11.1 Derivations

- Age at informed consent (years) = [(date of informed consent signature – date of birth + 1) / 365.25].

12. MEDICAL HISTORY CONDITIONS AND SURGERIES

Medical History information will be presented for the SAF. Medical History conditions and surgeries are captured in the “Medical History” CRF. Conditions will be presented based on CRF categories. Medical History captured as “Other, specify” on the CRF will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at time of locked database and presented in terms of system organ class (SOC) and preferred term (PT).

Additional details about lipodystrophy diagnosis will also be summarized:

- Age at lipodystrophy diagnosis
- Lipodystrophy subtype

See **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported.

12.1 Derivations

- Age at lipodystrophy diagnosis (years) = [(date of lipodystrophy diagnosis - date of birth + 1) / 365.25].

13. MEDICATIONS

Medications will be presented for the SAF and coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD) at database lock. Medications will be categorized as prior or concomitant, and the total number of patients in each category will be summarized by anatomic therapeutic class level 3 and preferred name.

If it is unclear whether or not a medication is prior or concomitant due to partial dates, the worst case will be assumed (i.e., concomitant). See **Appendix 1** for handling of partial dates.

- 'Prior' medications are medications which the patient started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which:
    - Started prior to, on or after the first dose of study medication and started no later than 14 days following end of study medication,
    - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

See **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported.

14. STUDY MEDICATION EXPOSURE

The summary of study drug exposure and compliance will be based on the SAF population. According to the protocol, patients should be encouraged to continue in the study and attend all protocol-specified visits until the end of the 3-year study period, even if discontinued from metreleptin, to enable continued evaluation of immunogenicity. Patients who discontinue metreleptin may restart treatment at any time during the 3-year study period. Therefore, duration of exposure will be presented in two ways: 1) total duration of exposure, and 2) duration of exposure accounting for interruptions.

The following will also be summarized: dose interruptions, dose reductions, and overdoses, as appropriate. An overdose is defined as a dose of metreleptin that exceeds the maximum dose of 10 mg/day for patients >40 kg (refer to the United States prescribing information) and is recorded in the CRF.

See **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported.

14.1 Derivations

- Total duration of exposure (days) = date of last study medication administration – date of first study medication administration + 1.
- Duration of exposure accounting for interruptions (days) = total duration – cumulative time off medication
    - Cumulative time off medication is the sum of time off medication over all medication interruptions.
    - Time off medication (days) = restart date – stop date - 1.

15. PRIMARY ANALYSIS – IMMUNOGENICITY

The primary immunogenicity analysis will be performed among the EAS. Analyses will be performed as described below. Additional data visualizations may be generated as needed.

15.1 Primary Analysis Variables

The primary objective is to evaluate the immunogenicity associated with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy. Immunogenicity will be described using the following variables:

- Anti-metreleptin/anti-HuL binding antibody measured by anti-drug antibody (ADA) titer
- Among ADA binding positive samples:
    - Category of *in vitro* neutralizing antibody (NAb) activity to metreleptin measured by cell-based assay titer
    - Receptor blocking* (RB) activity measured by electrochemiluminescence immunoassay (ECLIA)
        - Titer (dilution factor)
        - Percent inhibition at minimum required dilution (MRD)

**Referred to in the protocol as receptor binding*

15.2 Primary Analysis Description, Derivations, and Definitions

The presence of anti-drug antibodies will be screened using an ADA binding assay, which detects antibodies to both Metreleptin and HuL, and reported as follows:

- Positive/negative for ADA binding by study visit. Positive ADA is defined as ADA binding detected at MRD (1:10 dilution factor). Both 90% and 80% two-sided Clopper-Pearson exact CIs will be presented.
- ADA binding by study visit and titer (negative [no ADA binding detected at MRD], 1:10, 1:50, 1:250, 1:1250, 1:6250, 1:31250). Dilution factors greater than 1:31250 will not be examined.
- Ever ADA positive and time to ADA positivity. Time to ADA positive result (months) = [((date of first ADA positive result – date of baseline visit) + 1)/30.4].
- Peak ADA (defined as the measurement which detects ADA binding activity at the largest dilution factor) and time to peak ADA. Time to peak ADA (months) = [((date of peak ADA – date of baseline visit) + 1)/30.4].

In vitro NAb activity will be measured in a cell-based assay and categorized into A, B, C, D and E categories based on titer. Categorization will be performed by IQVIA Data Management and the resulting derived data will be provided to IQVIA RWE Biostatistics. Positive/negative for NAb activity, high positive NAb activity, and NAb titer categories will be presented by study visit along with two-sided 90% and 80% Clopper-Pearson exact CIs. The titer categories are defined as follows:

- If no activity is detected upon initial testing (1:80 dilution factor) with the cell-based assay, the result is reported as category A.
- If activity is detected at the initial test concentration, the sample is retested at the same concentration (1:80 dilution factor). If no activity is detected on retest, the initial result is attributed to assay noise, and the sample is reported as category B.
- If activity is detected on both tests at MRD, the sample is diluted and retested until activity is no longer detected. Depending on the number of dilutions required to dilute NAb activity below the detectable threshold, the result is reported as follows:
    - If no activity is detected at 1:800 dilution factor, then category C
    - If no activity is detected at 1:8000 dilution factor, then category D
    - If activity is detected at 1:8000 dilution factor, then category E. Dilution factors greater than 1:8000 will not be examined.

Positive NAb activity will be defined as a titer category C, D, or E result. High positive NAb activity will be defined as a a titer category D or E result. Category D and E results are considered to represent

high potency NAb activity. The clinical relevance of NAb activity results in any category has not been determined, and is a topic of current investigation. The following information will be summarized:

- Ever NAb positive and time to NAb positivity. Time to NAb positivity (months) = [((date of first NAb positive result – date of baseline visit) + 1)/30.4].
- Ever high NAb positive and time to high NAb positivity. Time to high NAb positivity (months) = [((date of first high~~t~~ NAb positive result – date of baseline visit) + 1)/30.4].
- Peak NAb (defined as the measurement which detects NAb activity at the largest dilution factor) and time to peak NAb. Time to peak NAb activity (months) = [((date of peak NAb – date of baseline visit) + 1)/30.4].

RB activity of anti-metreleptin/anti-HuL will be assessed by ECLIA receptor blocking assay and reported as follows:

- Positive/negative for RB activity by study visit. Positive RB activity is defined as RB activity detected at MRD (1:6 dilution factor). Both 90% and 80% two-sided Exact CIs will be presented.
- RB activity by study visit and titer (negative [no RB activity detected at MRD], 1:6, 1:30, 1:300, 1:3000). Dilution factors greater than 1:3000 will not be examined.
- Percent inhibition at MRD by study visit
- Ever RB positive and time to RB positivity. Time to RB positivity (months) = [((date of first RB positive result – date of baseline visit) + 1)/30.4].
- Peak RB (defined as the measurement which detects RB activity at the largest dilution factor) and time to peak RB. Time to peak RB result (months) = [((date of peak RB – date of baseline visit) + 1)/30.4].

See **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported.

16. SECONDARY ANALYSIS – IMMUNOGENICITY

The secondary objective of this study is to assess 2 methods of measuring *in vitro* neutralizing activity to metreleptin:

1. Cell-based assay
2. ECLIA receptor blocking assay

In vitro neutralizing activity as measured by cell-based and ECLIA receptor blocking assays are fully described by the primary analysis (**Section 15.** Primary Analysis – Immunogenicity). There will be no formal comparison of the two assay methods. No further analyses are required to achieve the secondary objective. Additional data visualizations may be generated as needed.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

17.1 Adverse Events

Adverse Events (AEs) will be coded using the latest version of MedDRA, and summarized by SOC, preferred name, and intensity. Intensity is captured in the CRF. See **Section 8.1** Statistical Tests and Confidence Intervals for a description of summaries to be reported.

Adverse Events of Special Interest (AESIs) are defined as:

- The presence of Category D or E *in vitro* cell-based NAb activity (or the relevant corresponding test result from the ligand-binding method) to metreleptin
- Necrotizing pancreatitis
- Hepatic adverse events including potential drug induced liver injury (DILI)
- Severe hypoglycemia
- Severe hypersensitivity reactions
- New diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis)
- Autoimmune disease exacerbation
- Serious infection resulting in hospitalization
- All cancers (excluding non-melanoma skin cancer) by cancer type
- Exposed pregnancies and pregnancy outcomes.

TEAEs are defined as AEs that started or worsened in severity on or after the first dose of study medication. If it is unclear whether or not an AE is a TEAE due to partial dates, the worst case will be assumed (i.e., TEAE). See **Appendix 1** for handling of partial dates.

AEs, serious AEs (SAEs), AEs of special interest (AESIs), TEAEs, AEs possibly caused by metreleptin, and AEs leading to metreleptin discontinuation will be summarized by ADA positivity and titer, cell-based NAb positivity and titer, and RB positivity, titer, and quintile of percent

inhibition. For each patient, only one event of each type will be selected to include in summary outputs. If a patient has multiple events the same type, the event with the highest severity level is selected. For patients with multiple events of the same type and severity, the event corresponding to the highest titer or percent inhibition level is selected. The corresponding titer and percent inhibition level are defined by the most recent measurement occurring prior to the event start date.

See **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported. Additional data visualizations may be generated as needed.

17.2 Physical Examination

Physical examination will be summarized by visit. The following information will be reported (see **Section 8.1** Statistical Tests and Confidence Intervals for a description of summaries to be reported):

- General Appearance (normal, abnormal, not done)
- Respiratory (normal, abnormal, not done)
- Cardiovascular (normal, abnormal, not done)
- Abdomen (normal, abnormal, not done)
- Skin (normal, abnormal, not done)
- Head and Neck (normal, abnormal, not done)
- Lymph Nodes (normal, abnormal, not done)
- Thyroid (normal, abnormal, not done)
- Musculoskeletal (normal, abnormal, not done)
- Neurological symptoms (normal, abnormal, not done)

17.3 Vital Signs

Vital signs will be summarized among adult patients (≥ 18 years at informed consent) by visit. The following vital signs measurements will be reported (see **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported):

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Temperature (^0C)
- Heart Rate (beats/min)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)

17.3.1 Derivations

- BMI (kg/m^2) = [Weight (kg)/(Height (cm)/100)^2].

17.4 Laboratory Evaluations

Clinical laboratory results (hematology, clinical chemistry, urinalysis, and lipid profile) will be summarized (see **Section 8.1** Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported) at each visit.

18. EXPLORATORY ANALYSES – EFFECTIVENESS

The exploratory analyses will be performed using the EAS population.

18.1 Exploratory Analysis Variables

The exploratory objective is to evaluate the effectiveness achieved with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy. The exploratory effectiveness variables are:

- hemoglobin A1c (HbA1c)
- fasting plasma glucose
- triglycerides
- leptin/metreleptin concentration

18.2 Exploratory Analysis Description, Derivations, and Definitions

Exploratory variables will be summarized using descriptive statistics (see **Section 8.1** Statistical Summaries, Tests and Confidence Intervals) and results will be presented as described below below:

- by visit
- as absolute change from baseline and percent change from baseline at each visit

HbA1c, fasting plasma glucose, and triglycerides will also be summarized by clinically relevant categories at each visit:

  - hbA1c (<8%, >=8%)
  - fasting plasma glucose (<70 mg/dL, >=70 mg/dL and <=100 mg/dL, <100 mg/dL)

- triglycerides (<500 mg/dl, >=500 mg/dl).

See Section 8.1 Statistical Summaries, Tests and Confidence Intervals for a description of statistics to be reported.

19. APPENDIX 1. PARTIAL DATE CONVENTIONS

As applicable, partial dates may be imputed for the purposes of categorizing medications as prior/concomitant and defining TEAs. Imputed dates will NOT be presented in listings. Conventions for imputing partial dates are described below. In general, partial date conventions are designed such that:

- If it is unclear whether or not a medication is prior or concomitant due to partial dates, the worst case will be assumed (i.e., concomitant).
- If it is unclear whether or not an AE is a TEAE due to partial dates, the worst case will be assumed (i.e., TEAE).

If a single medication or AE is reported more than once and partial date imputations cause the instances to appear overlapping, then the medication or AE will be assumed to be a single continuous instance. Start date will be assumed to be the earliest occurring started date (imputed or observed), and end date will be assumed to be the last occurring end date (imputed or observed).

Table 1: Algorithm for Imputing Partial Dates

Missing data element				Imputation rule
Start date or stope date?	**Day**	**Month**	**Year**	
Start Date	Yes	No	No	If the non-missing month is the same as the month of study medication start, impute study medication start date. Otherwise, impute the first day of the non-missing month.
Start Date	Yes	Yes	No	If the non-missing year is the same as the year of study medication start, impute study medication start date. Otherwise, impute the first day of the non-missing year (i.e., January 1st).

Start Date	Yes	Yes	Yes	Impute study medication start date.
Stop Date	Yes	No	No	If study discontinuation date occurred during the non-missing month, impute study discontinuation date. Otherwise, impute the last day of the non-missing month.
Stop Date	Yes	Yes	No	If study discontinuation date occurred during the non-missing year, impute study discontinuation date. Otherwise, impute the last day of the non-missing year (i.e., December 31st).
Stop Date	Yes	Yes	Yes	Impute study discontinuation date.

20. APPENDIX 2. WINDOWING CONVENTIONS

The below windowing conventions will be used to categorize all study assessments, including assessments occurring during unscheduled visits, into time periods of interest. Days are counted from the date of baseline visit where Baseline is defined as Day 0.

Only one assessment of each type will be presented from each analysis window. If more than one assessment of the same type occurs within an analysis window, then the maximum severity result will be selected for presentation. If more than one assessment of each types occurs within the maximum severity category, the result closest to the end of the analysis window will be selected. If the concept does not apply, then the result closest to the end of the analysis window will be selected.

The result closest to the end of the analysis window is preferred since the end of the analysis window aligns with the end of the visit window in all cases while the beginning of the analysis window may precede the beginning of the visit window. Therefore, the result closest to the end of the analysis window is most likely to be within the visit window.

Table 2: Windowing conventions

Study Visit	Study Month	Protocol Specified Visit Window	Analysis Window
Visit 1 (Screening)	Month -1	Day -28 to Day 0	Day ≤ -1
Visit 2 (Baseline)	Month 0	Day 0	Day 0
Visit 3	Month 1	Day 23 to Day 37	Day 1 to Day 37

Study Visit	Study Month	Protocol Specified Visit Window	Analysis Window
Visit 4	Month 2	Day 53 to Day 67	Day 38 to Day 67
Visit 5	Month 4	Day 114 to Day 128	Day 68 to Day 128
Visit 6	Month 6	Day 175 to Day 189	Day 129 to Day 189
Visit 7	Month 9	Day 266 to Day 280	Day 190 to Day 280
Visit 8	Month 12	Day 350 to Day 378	Day 281 to Day 378
Visit 9	Month 18	Day 533 to Day 561	Day 379 to Day 561
Visit 10	Month 24	Day 715 to Day 743	Day 562 to Day 743
Visit 11	Month 30	Day 898 to Day 926	Day 744 to Day 926
Visit 12	Month 36	Day 1080 to Day 1108	Day ≥ 927

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Brian Mangal b.mangal.consultant@chiesi.com Security Level: Email, Account Authentication (None)	DocuSigned by: Brian Mangal FA68091E7FAE42C... Signature Adoption: Pre-selected Style Using IP Address: 66.183.205.188	Sent: 3/14/2024 6:02:58 AM Resent: 3/19/2024 12:41:11 AM Viewed: 3/20/2024 6:52:33 AM Signed: 3/20/2024 6:52:46 AM
Electronic Record and Signature Disclosure: Accepted: 3/20/2024 6:52:33 AM ID: a060b1a1-2451-4018-8df2-c5701de3cbb5 Company Name: IQVIA		
Imaani Easthausen imaani.easthausen@iqvia.com Security Level: Email, Account Authentication (None)	DocuSigned by: Imaani Easthausen C8854A1FE2E8486... Signature Adoption: Pre-selected Style Using IP Address: 162.44.245.32	Sent: 3/14/2024 6:02:59 AM Viewed: 3/14/2024 6:03:48 AM Signed: 3/14/2024 6:03:54 AM
Electronic Record and Signature Disclosure: Accepted: 7/5/2023 10:40:01 PM ID: 6a3dec7a-0b89-4130-9ad3-99dfd386f4f5 Company Name: IQVIA		
Janet Boylan janet.boylan@chiesi.com Security Level: Email, Account Authentication (None)	DocuSigned by: Janet Boylan A5E2C5EA84644FC... Signature Adoption: Pre-selected Style Using IP Address: 78.152.221.250	Sent: 3/14/2024 6:02:59 AM Resent: 3/19/2024 12:41:12 AM Viewed: 3/28/2024 3:36:15 AM Signed: 3/28/2024 3:36:28 AM
Electronic Record and Signature Disclosure: Accepted: 3/28/2024 3:36:15 AM ID: 400f6e02-f0ce-43f3-93b7-743217482d53 Company Name: IQVIA		
Orla Casey orla.casey@chiesi.com Security Level: Email, Account Authentication (None)	DocuSigned by: Orla Casey 957E4F8B479F407... Signature Adoption: Pre-selected Style Using IP Address: 37.228.226.45	Sent: 3/14/2024 6:03:00 AM Resent: 3/19/2024 12:41:12 AM Viewed: 3/19/2024 10:58:15 PM Signed: 3/19/2024 10:59:13 PM
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Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	3/14/2024 6:03:00 AM
Certified Delivered	Security Checked	3/19/2024 10:58:15 PM
Signing Complete	Security Checked	3/19/2024 10:59:13 PM
Completed	Security Checked	3/28/2024 3:36:28 AM

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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

The timing of the change(s) was:

☒ After authorization (signed version) of the SAP but prior to the database lock/ interim data cut/ final Statistical Report/ Clinical Study Report (CSR)

☒ After database lock/ interim data cut/ final Statistical Report/ CSR

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

Describe the change(s) required:

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

Changes documented in 16Dec2024 version (prior to DBL)

1. Update definition of EAS from:
   [E]nrolled subjects who received at least one documented dose of metreleptin and who have baseline and post-dose laboratory results on the measure of interest at the time point of interest.

   To:
   Enrolled subjects who received at least one documented dose of metreleptin and who have at least one anti-metreleptin/anti-HuL binding antibody (Antidrug Antibody (ADA) binding) result.

2. Update the following analysis from:
   AEs, serious AEs (SAEs), AEs of special interest (AESIs), TEAEs, AEs possibly caused by metreleptin, and AEs leading to metreleptin discontinuation will be summarized by ADA positivity and titer, cell-based NAb positivity and titer, and RB positivity, titer, and quintile of percent inhibition.

   To:
   TEAEs, serious TEAEs, TEAEs that are AEs of special interest (AESIs), TEAEs possibly caused by metreleptin, and TEAEs leading to metreleptin discontinuation will be summarized by ADA positivity and titer, cell-based NAb positivity and titer, and RB positivity, titer, and quintile of percent inhibition.

3. Update analysis windows such that data collected for a CRF-defined visit are windowed according to the CRF-defined visit. Previously analysis windows ended on the same day as CRF-defined visit windows and extended CRF-defined windows to cover the calendar space since the last CRF-defined visit. Analysis windows are updated to extend CRF-defined visit windows to cover calendar space on either side of the CRF-defined visit window. See updated windows in Table 1 below.

Changes added 26Feb2025 (after DBL)

4. Treatment interruptions occurred for Patient 002002 from 07-Jun-2021 to 01-Jul-2021 and Patient 002003 from 22-Feb-2021 to 27-Feb-2021. These treatment interruptions were not recorded in the “Prescription Changes to Metreleptin” CRF, but were confirmed by the site investigator. These prescription changes will be hard coded. Request made by: Chiesi. Date of request: 21-Feb-2025.

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

Datasets/programs Impacted:

- Dataset: EX
- Program: EX.sas
- Program details: For subject "002002" - create extra rows for temporary drug interruption where start date is "2021-06-07" and end date is "2021-07-01". Also, for subject "002003" - create extra rows for temporary drug interruption where start date is "2021-02-22" and end date is "2021-02-27". The EXCAT for these new rows will be "PRESCRIPTION CHANGES TO METRELEPTIN". Set EXDOSE equals to 0 mg and for temporary interruption questionnaire (Did the prescription change result in a temporary interruption of treatment?) equals to “Yes”.
- Program log notes: `NH02/24/2025 : Create treatment interruption rows for Patient 002002 from 07-Jun-2021 to 01-Jul-2021 and Patient 002003 from 22-Feb-2021 to 27-Feb-2021 as confirmed by the site investigator under RSC dataset i.e. Prescription Changes to Metreleptin.`
- Implementer: Narek Hovhannisyan
- QC Programmer: Anita Panthi

TLFs Impacted:

- Table 1.6 – Metreleptin exposure (SAF)
  - Any temporary interruptions and number of temporary interruptions
  - Any dose reductions
  - Duration of exposure accounting for interruptions (months)
- Listing 12 – Prescription changes to metreleptin (SAF)
- Figure 6.2 – Patient 002002 Profile: Immunogenicity and effectiveness
- Figure 6.3 – Patient 002003 Profile: Immunogenicity and effectiveness

Impact on Interpretation of results:
Improves interpretability of results as confirmed data not included in database are presented in analyses.

5. Patients 002003 and 004004 had inconsistent results in RB samples at Visit 5 (Month 4) and Visit 4 (Month 2), respectively. Specifically, testing at the minimum required dilution (dilution factor = 6) with acid was positive at Tier 1 (initial test), but negative at Tier 2 (re-test). Given inconsistent results, these samples were

Client:	Chiesi
Protocol No.:	AEGR-734-401
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Date:	26-Feb-2025

removed from summary analyses using hard coding. Request made by: Chiesi. Date of request: 10-Jan-2025.

Datasets/programs Impacted:

- Dataset: ADIS
- Program: ADIS.sas
- Program details: If Subject '002003' and AVISIT is 'Month 4' then keep ANL02FL blank, In addition, if Subject '004004' and AVISIT is 'Month 2', then keep ANL02FL blank.
- Program log notes: [notes] `AP:2/11/2025 Update usubjid = 'AEGR-734-401-002003' and avisit = 'Month 4' and usubjid = 'AEGR-734-401-004004' and avisit = 'Month 2' analysis results as NOT REPORTABLE s these are inconsistent results as confirmed by sponsor.`
- Implementer: Anita Panthi
- QC Programmer: Nicolas Dalcero

TLFs Impacted:

- Table 4.1 - RB activity at MRD among ADA positive patients (EAS)
  - RB positivity by time point
- Table 4.2 - RB activity by titer among ADA positive patients (EAS)
  - RB titer by time point
- Table 4.3 - RB percent inhibition at MRD among RB positive patients (EAS)
  - RB percent inhibition at MRD by time point
- Table 4.4 - Ever RB positive and peak RB activity among ADA positive patients (EAS)
  - Time to RB positivity
  - Time to peak RB
- Figure 1.3 – RB activity by patient among ever ADA positive patients (EAS)
  - RB titer by timepoint
- Figure 6.3 – Patient 002003 Profile: Immunogenicity and effectiveness
  - RB titer by timepoint
- Figure 6.9 – Patient 004004 Profile: Immunogenicity and effectiveness
  - RB titer by timepoint

Impact on Interpretation of results:

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

Improves interpretability, because uninterpretable results are removed from summary analyses.

6. For patients 004004 and 004005, ADA samples were tested beyond the recommended number of freeze/thaw cycles. Re-analysis of aliquots with lower number of freeze/thaw cycles was possible, and study team agreed that the re-tested samples should be included in summary tables. As the algorithm used to select ADA results for inclusion in summary tables was already selecting the re-tested samples for inclusion in summary tables, no modifications were required. Request made by: Chiesi. Date of request: 11-Mar-2025.

   Datasets/programs Impacted: None.

   TLFs Impacted: None.

   Impact on Interpretation of results: No changes.

7. Treatment interruption for Patient 003001 was not recorded in Prescription Change Log, but was identified in AEs where action taken with metreleptin was recorded as “drug interrupted.” Treatment interruption start and end dates were imputed as start date of pregnancy (18-Jun-2020, AE ID: 1) and end date of miscarriage (23-Jul-2020, AE ID: 3).

   Datasets/programs Impacted:
   - Dataset: ADEX
   - Program: ADEX.sas
     Program details: For subject "003001" - create extra rows for temporary drug interruption where start date is "2020-06-18" and end date is "2020-07-23". The EXCAT for these new rows will be "PRESCRIPTION CHANGES TO METRELEPTIN". Set EXDOSE equals to 0 mg and for temporary interruption questionnaire (Did the prescription change result in a temporary interruption of treatment?) equals to “Yes”.Program log notes: `BN03/20/2025 : Create treatment interruption rows for Patient 003001 from 18-Jun-2020 to 23-Jul-2020 as confirmed by the site investigator under PRSC dataset i.e. Prescription Changes to Metreleptin.`
   - Implementer: Barbara Nogar
   - QC Programmer: Anita Panthi

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

TLFs Impacted:

- Table 1.6 – Metreleptin exposure (SAF)
  - Any temporary interruptions and number of temporary interruptions
  - Any dose reductions
  - Duration of exposure accounting for interruptions (months)
- Listing 12 – Prescription changes to metreleptin (SAF)
- Figure 6.2 – Patient 002002 Profile: Immunogenicity and effectiveness
- Figure 6.3 – Patient 002003 Profile: Immunogenicity and effectiveness

Impact on Interpretation of results:
Improves interpretability of results as data not included in database are presented in analyses.

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

Table 1: Updated Visit Windows

Study Visit	Study Month	Protocol Specified Visit Window	Analysis Window
Visit 1 (Screening)	Month -1	Day -28 to Day 0	Day ≤ -1
Visit 2 (Baseline)	Month 0	Day 0	Day 0
Visit 3	Month 1	Day 23 to Day 37	Day 1 to Day 44
Visit 4	Month 2	Day 53 to Day 67	Day 45 to Day 90
Visit 5	Month 4	Day 114 to Day 128	Day 91 to Day 151
Visit 6	Month 6	Day 175 to Day 189	Day 152 to Day 227
Visit 7	Month 9	Day 266 to Day 280	Day 228 to Day 314
Visit 8	Month 12	Day 350 to Day 378	Day 315 to Day 455
Visit 9	Month 18	Day 533 to Day 561	Day 456 to Day 637
Visit 10	Month 24	Day 715 to Day 743	Day 638 to Day 820
Visit 11	Month 30	Day 898 to Day 926	Day 821 to Day 1002
Visit 12	Month 36	Day 1080 to Day 1108	Day ≥ 1003

Describe the process used to decide on the change(s) and who was involved:

Changes documented in 16Dec2024 version (prior to DBL)
Discussed with client at meetings on 11Sep2024 and 14Oct2024.

Changes added 26Feb2025 (after DBL)
Discussed with client via email and at meetings on 06Feb2025 and 07Feb2025.

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

The group(s) responsible for the change(s) and implications for the study:

Changes documented in 16Dec2024 version (prior to DBL)
Imaani Easthausen – Statistical Team Lead, IQVIA
Petya Angelova – Medical Lead, IQVIA

Orla Casey –Translational and Immunogenicity , Chiesi
Janet Boylan – Head of Clinical Operations Chiesi
Inbar Aviezer– Associate Clinical Project Manager, Chiesi
Meng Wang – Statistician, Chiesi
Sue Schmidt – Consultant Immunogenicity Subject Matter Expert, Chiesi
Roberto Pierini – Immunogenicity Subject Matter Expert, Chiesi
Brian Mangal – Consultant Statistician, Chiesi

Changes added 26Feb2025 (after DBL)
Imaani Easthausen – Statistical Team Lead, IQVIA
Orla Casey –Translational and Immunogenicity , Chiesi
Janet Boylan – Head of Clinical Operations Chiesi
Inbar Aviezer– Associate Clinical Project Manager, Chiesi
Meng Wang – Statistician, Chiesi
Roberto Pierini – Immunogenicity Subject Matter Expert, Chiesi

Client:	Chiesi
Protocol No.:	AEGR-734-401
Project Code:	DYA76668
Date:	26-Feb-2025

Form completed by:

Title	Name	Signature	Date
Statistical Team Lead	Imaani Easthausen	DocuSigned by: Imaani Easthausen C8854A1FE2E8486...	15-Apr-2025

Form approved by:

Title/ Role	Name	Signature	Date
Senior Biostatistical Reviewer	Tracy Franklin	DocuSigned by: Tracy Franklin 8F7343FFCE2E433...	15-Apr-2025

Form approved by:

Title	Name	Signature	Date
Lead Epidemiologist	Shahrzad Salmasi	DocuSigned by: Shahrzad Salmasi 2C4282ADB1C54AC...	15-Apr-2025

Form approved by Client Representative (if applicable):

Title	Name	Signature	Date
Translational and Immunogenicity Lead	Orla Casey	DocuSigned by: Orla Casey 957E4F8B479F407...	24-Apr-2025
Head of Clinical Operations	Janet Boylan	DocuSigned by: Janet Boylan A5E2C5EA84644FC...	23-Apr-2025

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Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	4/15/2025 9:26:44 AM
Certified Delivered	Security Checked	4/15/2025 12:14:22 PM
Signing Complete	Security Checked	4/15/2025 12:14:29 PM
Completed	Security Checked	4/24/2025 10:55:17 AM

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Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	• Internet Explorer (Windows Only) 8.0 or above – compatibility mode is supported only for 9.0 and above. • Windows Edge Current Version • Mozilla Firefox Current Version • Safari (Mac OS only) 6.2 or above • Google Chrome Current Version
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

** These minimum requirements are subject to change. If these requirements change, we will provide you with an e-mail message at the e-mail address we have on file for you at the time the hardware and software requirements are revised.

Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

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