A 36-Month, Multicenter, Open Label Phase 4 Study to Evaluate the Immunogenicity of Daily SC Metreleptin Treatment in Patients with Generalized Lipodystrophy

Protocol AEGR-734-401

Aegerion Pharmaceuticals Inc.
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Medical Monitor: TBD
(CRO to be confirmed)

Biostatistician: TBD
(CRO to be confirmed)

Central Laboratory: TBD
(CRO to be confirmed)

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrolment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients. I agree to conduct this study in full accordance with all applicable regulations, guidelines, and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

Principal Investigator Name	Principal Investigator Signature	Date

SPONSOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein:

8 FEBRUARY 2018.

Alison Long MD PhD
Vice President, Clinical
Aegerion Pharmaceuticals, Inc.

Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
Anti-HuL	Anti human leptin
AST	Aspartate aminotransferase
βhCG	Beta human chorionic gonadotropin
CSA	Clinical Study Agreement
eCRF	Electronic case report form
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin
HuL	Human leptin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
ULN	Upper limit of normal
US/USA	United States (of America)
USPI	United States prescribing information

1. SYNOPSIS

<table>
<tr><td>NAME OF SPONSOR/COMPANY:</td><td>AEGERION PHARMACEUTICALS, INC.</td></tr>
<tr><td>Name of Finished Product:</td><td>MYALEPT</td></tr>
<tr><td>Name of Active Ingredient:</td><td>Metreleptin</td></tr>
<tr><td>Study Number:</td><td>Protocol AEGR-734-401</td></tr>
<tr><td>Title of Study:</td><td>A 36-Month, Multicenter, Open Label Phase 4 study to Evaluate the Immunogenicity of Daily SC Metreleptin Treatment in Patients with Generalized Lipodystrophy</td></tr>
<tr><td>Number of Investigators and Study Centers:</td><td>The study will be conducted at approximately 10 study centers in the United States (US).</td></tr>
<tr><td>Development Phase:</td><td>Phase 4</td></tr>
<tr><td>Objectives:</td><td>
<table>
<tr><th>Primary Objective:</th><th>Outcome Measure:</th></tr>
<tr><td>Evaluate the immunogenicity associated with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy.</td><td>Anti-metreleptin, anti human leptin (anti-HuL) binding antibody titers over time.
Category of in vitro neutralizing activity to metreleptin in a cell-based assay and titer in a receptor-binding assay in metreleptin/leptin- antibody positive samples over time.</td></tr>
<tr><th>Secondary Objective:</th><th>Outcome Measure :</th></tr>
<tr><td>Assess 2 methods of measuring in vitro neutralizing activity to metreleptin.</td><td>Receptor-binding assay titer, cell-based assay category.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><th>Safety Objectives:</th><th>Outcome Measure:</th></tr>
<tr><td>Evaluate the safety and tolerability in relation to the development of or absence of anti-metreleptin or anti-huL antibodies, and/or in vitro neutralizing activity to metreleptin in patients with congenital or acquired generalized lipodystrophy.</td><td>SAEs, adverse events leading to discontinuation, loss of response (as assessed by HbA1c and serum triglycerides), severe infections and/or sepsis, standard laboratory tests, and vital signs over time.</td></tr>
<tr><td>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.</td><td>Receptor-binding assay titer, cell-based assay category.</td></tr>
</table>
<table>
<tr><th>Exploratory Objective:</th><th>Outcome Measure:</th></tr>
<tr><td>Evaluate the efficacy achieved with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy.</td><td>Change from baseline in HbA1c and fasting triglycerides over time.</td></tr>
</table>
</td></tr>
<tr><td>Study Population</td><td>Patients who have been prescribed metreleptin for treatment of these conditions will be enrolled in the study, prior to initiation of metreleptin treatment. Pediatric patients will be included since patients with congenital generalized lipodystrophy present with this condition at birth and patients with acquired generalized lipodystrophy often present during early childhood.

Assessment of antibodies is required; thus, only patients who have not been previously treatment with metreleptin will be</td></tr>
</table>

	enrolled in order to document the development of antibodies over time.
Methodology/Study Design:	MYALEPT™ (metreleptin) has been approved as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy (MYALEPT Prescribing Information). This study is a multicenter, 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 the postmarketing requirement. Patients who have been prescribed metreleptin for lipodystrophy, who meet all enrollment criteria and sign 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 Months 1, 2, 4, 6, 9, 12, 18, 24, 30, and 36), for a total of 12 visits over 3 years (36 months). All patients with suspected loss of metreleptin efficacy (worsening of metabolic control) or endogenous leptin action (severe infections or sepsis) should be tested for *in vitro* neutralizing activity.
Planned Number of Patients:	Ten patients who have been prescribed metreleptin will be enrolled.
Study Population/ Inclusion Criteria:	For inclusion in the study, patients should fulfill the following criteria at the screening visit: 1. Provision of informed consent prior to any study specific procedures. If <18 years of age, has a parent or guardian able to read, understand, and sign the Informed Consent Form (ICF) and a Child Assent form, communicate with the Investigator, and understand and comply with protocol requirements. Adolescent patients must also read and understand the Child Assent Form. If the child is too young or unable to read, then the Child Assent form must be explained to the child. 2. Female and/or male patients ≥1 years of age.

	3. Physician-confirmed diagnosis of congenital or acquired generalized lipodystrophy and will begin treatment with MYALEPT for the first time. 4. Negative pregnancy test (urine or serum) for female patients of childbearing potential. 5. Female patients of childbearing potential must be 1 year postmenopausal, surgically sterile, or be willing to use an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent). In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used. 6. Male patients must be surgically sterile or be willing to use an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent). 7. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of metreleptin.
Exclusion Criteria:	Patients should not enter the study if any of the following exclusion criteria are fulfilled: 1. Involvement in the planning and/or conduct of the study (applies to both Aegerion staff and/or staff at the study site.) 2. Previous treatment with metreleptin. 3. Participation in another clinical study with an investigational product during the last 6 months. 4. Patients with prior severe hypersensitivity reactions to metreleptin or to any of the product components. 5. Known to have tested positive for human immunodeficiency virus, are immunocompromised, or are receiving immunomodulatory drugs. 6. Known history of drug or alcohol abuse within 1 year of screening. 7. Creatinine clearance <30 mL/min using institutional standards: e.g., calculated using Cockcroft-Gault formula for patients

<table>
<tr><td></td><td>≥18 years of age;
calculated using Schwartz equation for patients <18 years of age.
8. For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.
9. Any condition where, in the opinion of the Investigator, participation in this study may pose a significant risk to the patient or could render the patient unable to successfully complete the study.</td></tr>
<tr><td>Test Product, Dose, Dosage Form, Mode of Administration:</td><td>Patients who have been prescribed metreleptin and are enrolled in the study will be administered metreleptin once daily by SC injection at doses consistent with the US prescribing information (see table below). Based on clinical response (e.g., inadequate metabolic control) or other considerations (e.g., tolerability issues, or excessive weight loss, particularly in pediatric patients), the dose may be decreased or increased to the maximum dosage (see table below).
<table>
<tr><th>Baseline weight</th><th>Starting daily dose (injection volume)</th><th>Dose adjustments (injection volume)</th><th>Maximum daily dose (injection volume)</th></tr>
<tr><td>≤40 kg (male and female patients)</td><td>0.06 mg/kg (0.012 mL/kg)</td><td>0.02 mg/kg (0.004 mL/kg)</td><td>0.13 mg/kg (0.026 mL/kg)</td></tr>
<tr><td>Male patients >40 kg</td><td>2.5 mg (0.5 mL)</td><td>1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)</td><td>10 mg (2 mL)</td></tr>
<tr><td>Female patients >40 kg</td><td>5 mg (1 mL)</td><td>1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)</td><td>10 mg (2 mL)</td></tr>
</table></td></tr>
<tr><td>Duration of Treatment and Study Participation:</td><td>Development of neutralizing antibodies to metreleptin and HuL has been observed with metreleptin treatment. The time to the first sample in which Category D or E in vitro neutralizing activity was detected ranged from 20 weeks to 156 weeks following initiation of metreleptin treatment. In this study, immunogenicity will be assessed over 3 years (36 months) of continuous treatment to allow sufficient time to evaluate not only binding antibodies to metreleptin and HuL, but also potential in vitro neutralizing activity.</td></tr>
</table>

Statistical Methods:	There will be no hypothesis testing. All data will be summarized by descriptive statistics and/or listing. The following will be used for all analyses: Patients treated with a dose of metreleptin will be included in the safety and tolerability and patients with a post dose sample will be assessed for immunogenicity Patients treated with a dose of metreleptin and with baseline and postdose efficacy data will be included in the efficacy analyses.

2. INTRODUCTION

2.1 Background

Metreleptin is a recombinant analog of human leptin recently approved in the United States (US) as an adjunct to diet as replacement therapy to treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Antibodies to metreleptin develop in the majority of patients who are treated with metreleptin. Anti-metreleptin antibodies with *in vitro* neutralizing activity have been identified in a small number of patients treated with metreleptin (MYALEPT Prescribing Information). The consequences of these neutralizing antibodies are not well characterized, but may potentially include inhibition of endogenous leptin action and/or loss of metreleptin efficacy. Severe infection and/or worsening metabolic control have also been reported. Because of potential risks associated with the development of anti-metreleptin antibodies that neutralize endogenous leptin, metreleptin is available only through a restricted program: the MYALEPT Risk Evaluation and Mitigation Strategy (REMS) Program.

Assessment of binding (non-neutralizing) antibodies (based on immunoassay) as well as neutralizing activity to metreleptin (based on an *in vitro* cell-based assay) has been performed in 2 metreleptin development programs: obesity and lipodystrophy. Prospective assessment of antibody development was specified in the obesity development program and retrospective testing of available samples was conducted in the lipodystrophy program. Anti-metreleptin antibodies have been detected in 70 to 95% of patients who received metreleptin in clinical studies across both programs. Data from the obesity and lipodystrophy programs indicate that, in most patients, anti-metreleptin antibodies occur at a low level (titer), are detected within 4-8 weeks following initiation of treatment, reach a peak titer or plateau within 10 to 20 weeks, and tend to decrease over time despite chronic antigen presentation (due to continued metreleptin therapy), but generally do not disappear completely during therapy. It should be noted that data from the lipodystrophy program generally confirm these findings, but the time course of antibody development and peak titer in lipodystrophy patients is less well-defined due to inconsistent sampling across patients in the clinical studies. In both populations, a small number of patients developed very high anti-metreleptin antibody titers which, in some cases, was associated with *in vitro* metreleptin neutralizing activity.

To fill some of the void in understanding immunogenicity in patients with generalized lipodystrophy, assessment of the immunogenicity associated with metreleptin treatment in a relevant number of patients was included as a post-approval requirement in the US. The requirement included the following: 1) assessment of anti-metreleptin and anti-human leptin (anti-HuL) binding antibodies when responses peak, 2) assessment of neutralizing antibodies in samples that are confirmed positive for binding antibodies to leptin, and 3) testing for *in vitro* neutralizing activity in patients with loss of effect (worsening metabolic control) or loss of endogenous leptin action (severe infections or sepsis), as well as an analysis of clinical events, over time, associated with binding antibodies or neutralizing antibodies. This study is designed to provide data for these assessments.

2.2 Rationale for Study Design, Doses and Control Groups

This study is being conducted to satisfy a postmarketing requirement to assess the immunogenicity associated with metreleptin treatment. Because immunogenicity can only be evaluated in the context of drug treatment, the study is open-label and will characterize antibody and *in vitro* neutralizing activity over time and will compare safety and tolerability in patients with different antibody statuses (e.g., binding antibody titer, *in vitro* neutralizing activity category, in vitro neutralizing activity percent inhibition). Immunogenicity will be evaluated in the context of the prescribing information for MYALEPT; thus, the patient population and dosing will be per the US prescribing information (MYALEPT Prescribing Information).

Anti-metreleptin and anti-HuL binding antibody titers over time will be evaluated in order to establish a time course of antibody development and to assess the development of antibodies that recognize the endogenous protein. Because samples from a few patients treated with metreleptin have demonstrated *in vitro* neutralizing activity in an *in vitro* cell-based assay, *in vitro* neutralizing activity will also be assessed in all antibody positive samples. To provide an orthogonal method to evaluate potential *in vitro* neutralizing activity, all antibody positive samples will also be assessed using a ligand-binding assay.

Safety and tolerability of metreleptin associated with the development of, or absence of, antibodies will be evaluated. All adverse events (AEs) will be collected throughout the course of this study. Serious adverse events (SAEs), adverse events of special interest

(AESI) AEs leading to discontinuation, standard laboratory tests and vital signs will be collected over time and analyzed for any potential association with antibody status. See Section 8.2 for definitions of AEs and AESIs.

The study duration is based on following patients treated with metreleptin for a period of 3 years. In previous studies, the time to the first sample in which Category D or E *in vitro* neutralizing activity was detected ranged from 20 weeks to 156 weeks following initiation of metreleptin treatment; therefore, in order to gain a relevant assessment of the time course for development of *in vitro* neutralizing activity as well as to allow sufficient time to capture cases of *in vitro* neutralizing activity, 3 years of exposure to metreleptin was selected.

2.3 Benefit/Risk and Ethical Assessment

Native leptin is a hormone predominantly secreted by adipose tissue that informs the central nervous system of the status of energy stores in the body. In patients with generalized lipodystrophy, leptin deficiency, resulting from the loss of adipose tissue, contributes to excess caloric intake, which exacerbates the metabolic abnormalities leading to comorbid conditions including severe insulin resistance, diabetes, and hypertriglyceridemia. As reported in the USPI, MYALEPT is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Treatment with MYALEPT resulted in robust mean/median reductions in HbA1c, fasting glucose, and triglycerides at 1 year. The magnitude of these reductions was greater in patients with higher HbA1c, fasting glucose, and triglycerides prior to treatment (MYALEPT Prescribing Information).

T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with MYALEPT. The benefits and risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy should be considered.

Anti-metreleptin antibodies with *in vitro* neutralizing activity have been identified in patients treated with MYALEPT. The consequences of these neutralizing antibodies are not well characterized but could include inhibition of endogenous leptin action and/or loss of MYALEPT efficacy. Severe infection and/or worsening metabolic control have been reported.

3. STUDY OBJECTIVES

3.1 Primary Objective

Primary Objective:	Outcome Measure:
Evaluate the immunogenicity associated with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy.	Anti-metreleptin, anti-HuL binding antibody titers over time. Category of *in vitro* neutralizing activity to metreleptin in a cell-based assay and titer in receptor-binding assay in metreleptin/leptin- antibody positive samples over time.

3.2 Secondary Objectives

Secondary Objective:	Outcome Measure:
Assess 2 methods of measuring *in vitro* neutralizing activity to metreleptin.	Receptor-binding assay titer, cell-based assay category.

3.3 Safety Objectives

Safety Objectives:	Outcome Measure:
Evaluate the safety and tolerability in relation to the development of or absence of anti-metreleptin or anti-huL antibodies, and/or *in vitro* neutralizing activity to metreleptin in patients with congenital or acquired generalized lipodystrophy. 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.	SAEs, adverse events leading to discontinuation, loss of response (as assessed by HbA1c and serum triglycerides), severe infections and/or sepsis, standard laboratory tests, and vital signs over time. Receptor-binding assay titer, cell-based assay category.

3.4 Exploratory Objectives

Exploratory Objective:	Outcome Measure:
Evaluate the efficacy achieved with daily SC metreleptin treatment in patients with congenital or acquired generalized lipodystrophy.	Change from baseline in HbA1c and fasting triglycerides over time.

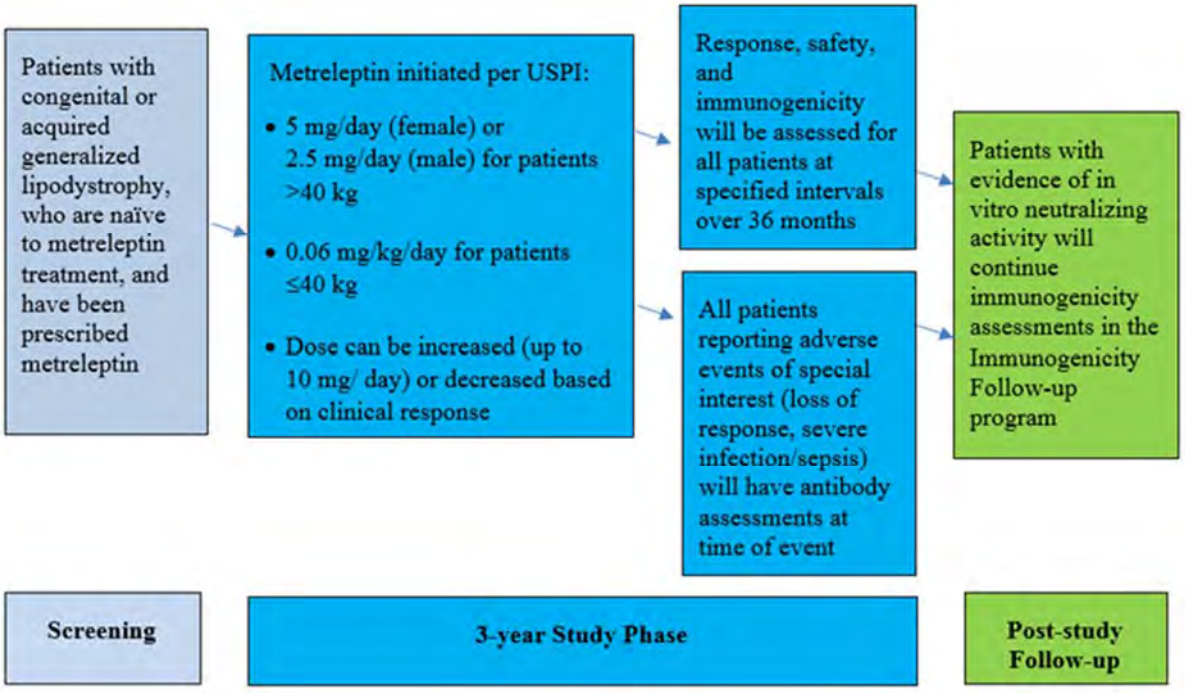
4. INVESTIGATIONAL PLAN

4.1 Study Design

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). Patients with *in vitro* neutralizing activity should enroll in the Immunogenicity Follow-up Program; refer to Section 7.3.3 for definitions of *in vitro* neutralizing activity categories.

Figure 1: Study Schematic



4.2 Number of Patients

Ten patients who have been prescribed MYALEPT will be enrolled.

4.3 Inclusion Criteria

For inclusion in the study, patients should fulfill the following criteria at the screening visit:

1. Provision of informed consent prior to any study specific procedures. If <18 years of age, has a parent or guardian able to read, understand, and sign the Informed Consent Form (ICF) and a Child Assent form, communicate with the Investigator, and understand and comply with protocol requirements. Adolescent patients must also read and understand the Child Assent Form. If the child is too young or unable to read, then the Child Assent form must be explained to the child.
2. Female and/or male patients ≥1 years of age.
3. Physician-confirmed diagnosis of congenital or acquired generalized lipodystrophy and will begin treatment with MYALEPT for the first time.
4. Negative pregnancy test (urine or serum) for female patients of childbearing potential.
5. Female patients of childbearing potential must be 1 year postmenopausal, surgically sterile, or be willing to use an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent). In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.
6. Male patients must be surgically sterile or be willing to use an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent).
7. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of metreleptin.

4.4 Exclusion Criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both Aegerion staff and/or staff at the study site.)
2. Previous treatment with metreleptin.

3. Participation in another clinical study with an investigational product during the last 6 months.
4. Patients with prior severe hypersensitivity reactions to metreleptin or to any of the product components.
5. Known to have tested positive for human immunodeficiency virus, are immunocompromised, or are receiving immunomodulatory drugs.
6. Known history of drug or alcohol abuse within 1 year of screening.
7. Creatinine clearance <30 ml/min using institutional standard:
   e.g., calculated using Cockcroft-Gault formula for patients ≥18 years of age;
   calculated using Schwartz equation for patients <18 years of age.
8. For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.
9. Any condition where, in the opinion of the Investigator, participation in this study may pose a significant risk to the patient or could render the patient unable to successfully complete the study.

For procedures for withdrawal of incorrectly enrolled patients, see Section 4.6.

4.5 Patient Enrollment and Randomization

Patients will not be randomized in this study. Patients who have been prescribed metreleptin will be screened for enrollment.

Investigator(s) should keep a record (the patient screening log) of patients who entered screening.

The Investigator(s) will:

- Obtain certification under the REMS for MYALEPT to prescribe MYALEPT.
- Confirm the patient meets the requirements for MYALEPT prescription, as per the USPI.
- Obtain signed informed consent from the potential patient or his/her guardian/legal representative before any study-specific procedures are performed.
- Assign potential patient a unique enrollment number.
- Determine patient eligibility (see Sections 4.3 and 4.4).
- Schedule Enrollment/Baseline visit to coincide with treatment initiation.

If a patient withdraws from participation in the study, then his/her enrollment code cannot be reused.

4.6 Procedures for Handling Incorrectly Enrolled Patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. If, however, the patient meets eligibility criteria at a later date they can be evaluated and enrolled on a case by case basis. If patients are enrolled but subsequently found not to meet all the eligibility criteria, the Investigator should consult with the Aegerion medical monitor to determine if continued participation poses a risk to the patient.

4.7 Methods for Assigning Treatment Groups

Patients will not be randomized; patients who meet all inclusion/exclusion criteria will be included in the study.

4.8 Methods for Ensuring Blinding

This section is not applicable. The study is open-label.

4.9 Methods for Unblinding

This section is not applicable. The study is open-label.

4.10 Restrictions

Patients must abstain from donating blood/plasma from the time of informed consent to end of study.

Patients should adhere to dietary instructions provided by their physicians (e.g., low-fat diet).

4.11 Discontinuation of Metreleptin

Patients may be discontinued from metreleptin in the following situations:

- Patient decision. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment.
- Investigator decision due to an AE.

- Investigator decision due to severe noncompliance.

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.

4.11.1 Procedures for Discontinuation of a Patient from Metreleptin

At any time, patients are free to discontinue metreleptin, without prejudice to further treatment. When discontinuing metreleptin in patients with risk factors for pancreatitis (e.g., history of pancreatitis, severe hypertriglyceridemia), tapering of the dose over a 1-week period is recommended. During tapering, triglyceride levels should be monitored and initiation of or adjustment of the dose of lipid-lowering medications should be considered, as needed. Signs and/or symptoms consistent with pancreatitis should prompt an appropriate clinical evaluation.

A patient who decides to discontinue metreleptin will be asked about the reason(s) and to specify any AEs or SAEs leading to discontinuation. If possible, patients should be seen and assessed by the Investigator(s). Adverse events will be followed up (see Section 8). Patients should return for all protocol-specified visits to allow for continued assessments, even if metreleptin has been discontinued. In addition to AESIs (refer to Section 8.3.8) and SAEs, samples for antibodies and *in vitro* neutralizing activity should be collected after discontinuation of metreleptin.

Patients who discontinue metreleptin may restart treatment at any time during the 3-year study period.

If a patient is withdrawn from the study, see Section 4.12.

4.12 Criteria for Withdrawal from the Study

4.12.1 Screen Failures

Screening failures are patients who sign the ICF but do not fulfill the eligibility criteria for the study and therefore must not be enrolled. Patients are allowed to be rescreened and enrolled into the study if they are found to be eligible at a later date. Patients who fail the screening process should have the reason for study withdrawal recorded as

"patient does not meet the required inclusion/exclusion criteria." This reason for withdrawal from study is only valid for screen failures and not for enrolled patients.

4.12.2 Withdrawal of the Informed Consent

Patients are free to withdraw from the study at any time (metreleptin and assessments), without prejudice to further treatment. In this case, the Investigator should provide a statement, in writing, that the patient declines all further follow-up. A patient who has withdrawn from the study is allowed to reenter the study and restart treatment any time during the 3-year study period, provided they still meet all inclusion criteria and none of the exclusion criteria.

A patient who withdraws consent will always be asked about the reason(s) and to specify any AEs or SAEs leading to withdrawal. The Investigator will follow up AEs/SAEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrollment code cannot be reused. Withdrawn patients will be replaced if time from enrollment to withdrawal is less than 6 months.

4.13 Discontinuation of the Study

The study may be stopped if, in the judgment of Aegerion, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the electronic case report form (eCRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

5. STUDY PLAN AND TIMING OF PROCEDURES

The Study Plan is presented in Table 1.

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

6. STUDY PROCEDURES

6.1 Schedule of Assessments

Study procedures are summarized in Table 1. Detailed descriptions of the efficacy, PK, and safety procedures to be conducted during this study are provided in the following sections.

Table 1: Schedule of Study Assessments

VISIT NUMBER	SCREENING 1	2	3	4	5	6	7	8	9	10	11	12	FOR DETAILS, SEE PROTOCOL SECTION:
MONTH	-1	0	1	2	4	6	9	12	18	24	30	36	
WINDOW (DAYS)	-28 TO 0	±0	±7	±7	±7	±7	±7	±14	±14	±14	±14	±14	
PROCEDURE													
Informed Consent and Assent	X												
Demographics	X												
Medical/Surgical History	X	X											
Inclusion/Exclusion criteria	X	X											
Physical Examination,	X							X		X		X	
Vital Signs/ Weight/ Height[a]	X	X	X	X	X	X	X	X	X	X	X	X	
Serum or Urine Pregnancy Test[b]	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting Samples for Hematology & Clinical Chemistry	X	X				X		X	X	X		X	
HbA1c, Lipids, Fasting Glucose	X	X	X	X	X	X	X	X	X	X	X	X	
Samples for Antibody and Leptin Measurements[c]		X	X	X	X	X	X	X	X	X	X	X	

VISIT NUMBER	SCREENING 1	2	3	4	5	6	7	8	9	10	11	12	FOR DETAILS, SEE PROTOCOL SECTION:
MONTH	**-1**	**0**	**1**	**2**	**4**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	
WINDOW (DAYS)	**-28 TO 0**	**±0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	
PROCEDURE													
Urinalysis	X							X		X		X	
Study Medication Administration First Dose		X											
Adverse Events, including SAEs and AESI		Continuous Monitoring											
Concomitant use of Lipid-Lowering, Antidiabetic and Immunomodulatory Agents	X	X	X	X	X	X	X	X	X	X	X	X	

a For all pediatric patients (≤18 years of age), a pubertal development assessment should also be conducted at Screening and Months 12, 24, and 36.
b A serum or urine pregnancy test (βhCG) should be completed for all female patients of child-bearing potential, unless the patient has had a hysterectomy.
c Samples for antibody measurement should be taken before administering metreleptin at each study visit in order to minimize high levels of metreleptin in the samples, which could interfere with antibody testing.

6.2 Enrollment/Screening Period

6.2.1 Screening

At screening, consenting patients will be assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

- The Informed Consent and HIPAA Authorization forms, will be signed prior to performing any protocol-required procedures. The following will be conducted at the Screening Visit:
- Inclusion and exclusion criteria will be verified.
- Body weight and height will be measured as part of a complete physical exam.
- The patient's complete medical/surgical history will be recorded.
- All prior medications (prescription medications within 3 months) and current medications will be reviewed; concomitant use of lipid-lowering and antidiabetic will be recorded in the eCRF.
- Vital signs (sitting systolic and diastolic blood pressure and heart rate) will be measured.
- Urine will be collected for urinalysis.
- A serum or urine pregnancy test (βhCG) will be conducted for all female patients of childbearing potential.
- Fasting blood samples will be collected for the following assessments:
    - Chemistry and hematology.
    - HbA1c, lipids, and fasting glucose.

When all the screening results are available, individuals will be notified by telephone of their eligibility status. Those who qualify will be eligible to return to the clinical study site within 28 days after the Screening Visit to complete eligibility requirements for enrollment.

Prior to the Enrollment Visit (Visit 2), the Investigator should obtain certification under the REMS for MYALEPT to enable prescribing of metreleptin. Once the prescription for metreleptin is filled, the physician should have the first drug shipment sent to the physician's office in preparation for the Enrollment Visit.

6.2.2 Baseline/Enrollment Visit

At the Enrollment Visit (Visit 2), to be conducted within 28 days of the Screening Visit, patients are to have fasted overnight (8 hours). Patients should delay administering their morning dose of anti-diabetes therapy (if applicable) until enrollment procedures have been completed. All procedures specified in the Study Plan (Table 1) should be conducted prior to first administration of metreleptin. The following will be conducted at the Baseline/Enrollment visit:

- Inclusion and exclusion criteria will be verified.
- Blood samples for measurement of leptin and antibodies to metreleptin and human leptin will be collected to provide a measurement prior to initiation of metreleptin.
- Fasting samples for hematology and clinical chemistry will be collected.
- Samples for measurement of HbA1c, lipids and fasting glucose will be collected.
- Vital signs and weight will be measured.
- Concomitant use of lipid-lowering and anti-diabetic, will be reviewed.
- The Investigator will instruct the patient on proper reconstitution of metreleptin and have the patient or caregiver administer the first dose of metreleptin by SC injection under observation.
- Serious adverse events and AESI (refer to Section 8.3.8) will be reviewed.
- Urine pregnancy tests (βhCG) will be conducted for all female patients of childbearing potential.

6.3 Treatment Period

After the first dose of metreleptin is administered at Visit 2 (Month 0), patients will complete Visits 3 to 12 at Months 1, 2, 4, 6, 9, 12, 18, 24, 30, and 36. Descriptions of the procedures for this period are included in the Study Plan (Table 1); all procedures should be conducted prior to administration of metreleptin on the day of the study visit. The following will be conducted during the treatment period:

- Blood samples for measurement of leptin and antibodies to metreleptin and human leptin will be collected.
- Samples for measurement of HbA1c, lipids and fasting glucose will be collected.
- Fasting samples for hematology and clinical chemistry will be collected (only at Visits 6, 8, 9, 10, and 12).

- Vital signs and weight will be measured.
- A physical examination, including height, will be conducted at Visits 8, 10, and 12.
- Concomitant use of lipid-lowering and antidiabetic, will be reviewed.
- Urine will be collected for urinalysis (only at Visits 8, 10, and 12).
- Urine pregnancy tests (βhCG) will be conducted for all female patients of childbearing potential.
- Serious adverse events and AESI (refer to Section 8.3.8) will be reviewed.

All Visit 12 assessments should be conducted for patients who discontinue the study prior to Month 36.

6.4 Follow-up for Patients with *In Vitro* Neutralizing Activity

Patients identified with neutralizing activity during the 3-year study period will be encouraged to continue participation in the study and complete all protocol-specified assessments until the end of the study period (even if the decision is made to discontinue metreleptin). At the end of the 3-year study period, these patients should be enrolled in the separate MYALEPT Immunogenicity Follow-up program in order to continue immunogenicity assessments. Evidence of *in vitro* neutralizing activity will be considered either Category D or E results in the cell-based assay (refer to Section 7.3.3), or positive results based on percent inhibition (criteria to be determined) in the receptor-binding assay (refer to Section 7.3.2). Instructions for consent and enrollment into this separate Follow-up program will be provided by the Sponsor's safety physician.

7. STUDY ASSESSMENTS

The Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRF. A copy of the completed eCRFs will be archived at the study site.

The sequence for the blood sampling tubes and the amount of blood drawn is found in Table 2. A smaller total volume is specified for patients weighing 40 lbs. or less.

Table 2: Blood Sample Tubes Volumes and Sequence

LAB TEST	TUBE	MINIMUM VOLUME REQUIRED (ML) PATIENTS 40 LBS. OR LESS	VOLUME FOR PATIENTS 41 LBS. OR MORE
Chem 10	Red Top	0.6	0.6
Lipid	Red Top	0.6	0.6
CBC/Hem	Lavender Top	0.5	0.5
HbA1c	Lavender Top	2	7
Antibody and Leptin	Gold SST	4	4
	Total Vol Collected:	7.7	12.7

7.1 Efficacy Assessments

Blood samples for measurement of HbA1c (%), fasting glucose (mg/dL), and triglycerides (mg/dL) will be collected at the times specified in the Study Plan (Table 1).

7.2 Safety Assessments

7.2.1 Laboratory Safety Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be collected at the times specified in the Study Plan (Table 1).

Laboratory variables to be measured are presented in Table 3:

Table 3: Laboratory Safety Variables

Hematology/hemostasis (whole blood)	**Clinical chemistry (serum)**
Hemoglobin (Hb)	Creatinine
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	Alkaline phosphatase (ALP)
Platelet count	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis (dipstick; microscopic if abnormal)	**Albumin**
U-Hb/Erythrocytes/Blood	Potassium
U-Protein/Albumin	Calcium, total
U-Glucose	Sodium

The Investigator should make an assessment of the available laboratory results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the study site as source data for laboratory variables. Refer to Section 8.3 for reporting of AEs based on laboratory test results.

If a patient has an AST **or** ALT ≥3x upper limit of normal (ULN) **and** total bilirubin ≥2x ULN, refer to Appendix B for further instruction in cases of combined increase of aminotransferase and total bilirubin

7.2.2 Physical Examination

A complete physical examination will be performed at the times specified in the Study Plan (Table 1) and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities), and neurological systems.

For all pediatric patients (≤18 years of age), a Tanner pubertal development assessment should be conducted at Visits 8, 10, and 12.

7.2.3 Vital Signs

Vital sign measurements will include sitting systolic and diastolic blood pressure and heart rate and body temperature. Vital signs and sitting blood pressure and pulse rate should be measured after the patient rests for approximately 5 minutes and with the patient in a sitting position. The blood pressure measurement should be repeated after at least 30 seconds and the average of the 2 readings recorded.

7.3 Immunogenicity

7.3.1 Collection of Samples for Measurement of Antibodies to Metreleptin and Leptin and *In Vitro* Neutralizing Activity

Blood samples for the measurement of antibodies to metreleptin and human leptin will be collected at the times specified in the Study Plan (Table 1). A cell-based assay and a receptor-binding assay will be used to measure *in vitro* neutralizing activity in all samples that test positive for antibodies to metreleptin and/or leptin (titer ≥5). The study lab manual will provide specific instructions for collection, processing, packaging, and shipping of all samples.

Additional safety samples for measurement of antibodies to metreleptin and human leptin will be collected if clinically indicated (e.g., loss of response to MYALEPT, or if patient develops a severe infection and/or sepsis), or at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

7.3.2 Determination of Antibodies to Metreleptin and Leptin

A Receptor Binding Electrochemiluminescent Immunoassay (ECLIA) Procedure for the Detection of Neutralizing Antibodies to Metreleptin and Leptin in Human Serum has been developed and validated to detect antibodies to both endogenous leptin and metreleptin (this method was previously submitted and approved by the FDA as part of our post-marketing commitments).

Antibodies to metreleptin are detected using a bridging ELISA format method. Full details of this method will be described in a separate report.

7.3.3 Determination of Metreleptin *In Vitro* Neutralizing Activity

There are no clinical indicators clearly associated with *in vitro* neutralizing activity; detection of neutralizing activity is achieved using an *in vitro* cell-based assay method. If no activity is detected upon initial testing 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, and 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 initial concentration, the sample is diluted and retested until activity is no longer detected. Depending on the number of dilutions required to dilute activity below the detectable threshold, the result is reported as Category C, D, or E. Category D and E results are considered to represent high potency *in vitro* neutralizing activity. The clinical relevance of *in vitro* neutralizing activity results in any category has not been determined, and is a topic of current investigation.

In addition, the receptor binding Electro-chemiluminescence (ECLIA) Procedure for the detection of neutralizing Antibodies to Metreleptin and Leptin in Human Serum has been developed and validated to detect antibodies to both endogenous leptin and metreleptin (this method was previously submitted and approved by the FDA as part of Aegerion's post-marketing commitments). The results are reported as percent inhibition and 80% inhibition is currently utilized as the neutralizing antibody threshold.

7.4 Pharmacokinetics

No formal pharmacokinetic (PK) analyses of metreleptin will be conducted; leptin concentrations will be measured.

7.4.1 Collection of Samples for Measurement of Leptin

Blood samples for the measurement of leptin will be collected at the times specified in the Study Plan (Table 1). The centralized laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

Additional safety samples for measurement of leptin will be collected if clinically indicated (e.g., loss of response to MYALEPT, or if patient develops a severe infection and/or sepsis), or at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

7.4.2 Determination of Leptin Concentration

Samples for determination of leptin concentration in plasma will be analyzed by a local laboratory using an appropriate bioanalytical method. Full details of the analytical methods used will be described in a separate bioanalytical report.

7.4.3 Storage and Destruction of Pharmacokinetic Samples

Any residual back-up PK samples may be used for future exploratory biomarker research or in the development of the ligand-binding assay. PK samples may be disposed of after finalization of the Bioanalytical Report, unless further analyses are necessary.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

7.5 Pharmacodynamics

Pharmacodynamic samples will not be evaluated in this study.

7.6 Pharmacogenetics

Pharmacogenetic samples will not be taken during the study.

7.7 Biomarker Analysis

No biomarkers, with the exception of those described in Table 1, will be analyzed.

8. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

All adverse events, including SAEs, adverse events leading to discontinuation, and AESIs will be recorded on the eCRF. Additionally, all SAE and AESI that require immediate reporting will be captured on the SAE/AESI form and sent to the pharmacovigilance department (see Section 8.6).

8.1 Definition of Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the clinically significant abnormal results of an investigation (e.g., laboratory findings). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

8.2 Definitions of Serious Adverse Events

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, wash-out, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, refer to Appendix A.

In addition, for the purposes of this protocol, the following adverse events of special interest (AESI) must be handled as SAEs and are reportable to Aegerion or designee (see Section 8.6) within the SAE timeframe regardless whether the adverse events did not meet the serious criteria described above in this section:

- The presence of Category D or E *in vitro* neutralizing activity (or the relevant corresponding test result from the ligand-binding method) to metreleptin
- Necrotizing pancreatitis
- Hepatic adverse events including potential DILI

- Severe hypoglycaemia
- 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

8.3 Recording of Adverse Events

8.3.1 Time Period for Collection of Adverse Events

Adverse events (AE), including serious adverse events (SAE), AEs leading to discontinuation and AESIs will be recorded from the signing of the informed consent or if the AE or AESI is related to study procedure.

8.3.2 Follow-up of Unresolved Adverse Events

Any SAEs, AEs leading to discontinuation and AESIs that are unresolved at the patient's last assessment as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. Aegerion retains the right to request additional information for any patient with ongoing AE/SAE(s) at the end of the study, if judged necessary.

8.3.3 Variables

The following variables will be collected for each AE leading to discontinuation and AESI:

- AE (verbatim)
- Date and time when the AE started and stopped
- Maximum intensity
- Maximum common terminology criteria for AE grade
- Whether the AE is serious or not

- Investigator causality rating against metreleptin (yes or no)
- Action taken with regard to metreleptin
- AE led to patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Reason AE is serious
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria presented in Section 8.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria in Section 8.2.

Intensity rating scale to be used:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

8.3.4 Causality Collection

The Investigator will assess causal relationship between metreleptin and each AE with the answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by metreleptin?'

The causal relationship will also be assessed for other medications and study procedures.

A guide to the interpretation of the causality question is provided in Appendix A.

8.3.5 Adverse Events Based on Signs and Symptoms

All adverse events, including SAEs, AEs leading to discontinuation, or AESIs spontaneously reported by the patient or care provider, or are reported in response to the open question from the study personnel or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) over recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.6 Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration, as compared to baseline, in protocol-mandated laboratory values and vital signs should be reported as.

8.3.7 Any new or aggravated clinically significant abnormal medical finding at a physical examination as compared with the baseline assessment should also be reported. Hy's Law

Cases where a patient has an AST or ALT ≥3x ULN and total bilirubin ≥2x ULN may need to be reported as SAEs. Refer to Appendix B for further instruction in cases of combined increase of aminotransferase and total bilirubin.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest will be collected and recorded in the eCRF.

A sample should be collected for measurement of *in vitro* neutralizing activity in all patients with the following AEs of special interest: suspected loss of response (worsening of metabolic control) or suspected loss of endogenous leptin action (severe infections or sepsis).

For patients who become pregnant during the study, a sample should also be collected to measure *in vitro* neutralizing activity at the time the pregnancy is identified. The patient

will be allowed to continue in the study; however, the decision as to whether to continue metreleptin therapy during the pregnancy will be at the discretion of the treating physician. The pregnancy and all pregnancy outcomes should be reported as an AESI and followed by the patients' prescribing physician.

8.4 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

Should an SAE occurs during the course of the study, Investigators or other site personnel must inform Aegerion or designee per Section 8.6 within 1 day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Aegerion representative or designee will work with the Investigator to ensure that all the necessary information is provided to the Aegerion Patient Safety data entry site **in a timely manner** for fatal and life-threatening events of initial receipt for all other SAEs.

For all SAEs, including fatal or life-threatening ,where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Aegerion representatives or designee of any follow-up information on a previously reported SAE within 1 calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

8.5 Overdose

An overdose is considered a dose of metreleptin that exceeds the maximum dose of 10 mg/day for patients >40 kg (refer to the US prescribing information) and should be recorded on the AE CRF when an AE is associated with the overdose. If no AE is associated with the overdose, the event should be recorded on the Overdose CRF.

- An overdose with associated SAEs is recorded as the SAE diagnosis/symptoms on the relevant SAE modules in the eCRF and on the Overdose eCRF module.

If an overdose on an Aegerion study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate Aegerion representatives or designee immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated Aegerion representative or designee works with the Investigator to ensure that all relevant information is provided to the Aegerion Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section8.4. For other overdoses, reporting must occur within 30 days.

8.6 Reporting Adverse Events

The principal investigator or site personnel are responsible for detecting, documenting, and reporting all events that meet the definition of an AE or SAE.

All SAEs and unanticipated events, occurring after the signing of the ICF up until either the scheduled Follow-up Visit or at least 4 weeks after the last dose of study medication in the case of an early termination, and regardless of study medication relationship, must be reported via email or by fax to Aegerion or designee within 24 hours of investigator awareness of the event on the SAE/AESI form.

Serious Adverse Event Contact Information:

Email: AegerionPV@ubc.com

Facsimile: US +1 877 200 2781

Facsimile: Rest of World +41 22 596 44 46

This form will capture data surrounding the event, e.g., the nature of the symptom(s), time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued. The principal investigator's assessment of causal assessment of the event to metreleptin exposure will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures as well as all pertinent medical information related to the event will be collected.

Should there be incomplete or missing information, Aegerion or designee will forward SAE queries directly to the investigator requesting additional information. It is the investigator's responsibility to be diligent in providing this information to Aegerion or designee as soon as it is available. Initial reports of SAEs should never be left on telephone voicemails.

8.7 Pregnancy

Any pregnancy that occurs during study participation must be reported as an AESI via the safety monitoring system described above. If a patient becomes pregnant, they will be allowed to continue in the study; however, the decision as to whether to continue metreleptin therapy during the pregnancy will be at the discretion of the treating physician.

Information related to pregnancy will be collected using the appropriate sections of the eCRF. The pregnancy will be followed to determine the outcome. At the end of the pregnancy, information on the status of the mother and child will be collected.

8.8 Management of Metreleptin-related Toxicities

There have been reports of generalized hypersensitivity (e.g., urticaria or generalized rash) in patients taking metreleptin. If a hypersensitivity reaction occurs, patients should discuss the proper clinical treatment for the event(s), including possible discontinuation of metreleptin with the Investigator.

Dosage adjustments, including possible large reductions, of insulin or insulin secretagogue (e.g., sulfonylurea) may be necessary in some patients to minimize the risk of hypoglycemia.

Refer to the USPI for further details (MYALEPT Prescribing Information).

9. METRELEPTIN AND OTHER TREATMENTS

9.1 Metreleptin

No study medication will be provided for this trial; patients who have been prescribed metreleptin will be included in the study and will receive the prescribed dosage of metreleptin as indicated in the USPI.

9.2 Dose and Treatment Regimens

Based on clinical response (e.g., inadequate metabolic control) or other considerations (e.g., tolerability issues, excessive weight loss [especially in pediatric patients]), the dose of metreleptin may be decreased or increased to the maximum dosage as summarized in Table 4; refer to the USPI for further details.

Table 4: MYALEPT Recommended Dosage

BASELINE WEIGHT	STARTING DAILY DOSE (INJECTION VOLUME)	DOSE ADJUSTMENTS (INJECTION VOLUME)	MAXIMUM DAILY DOSE (INJECTION VOLUME)
Patients ≤40 kg (males and females)	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)
Male patients >40 kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
Female patients >40 kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)

9.3 Labeling

No labels will be prepared for this study. Patients will receive commercially available metreleptin.

9.4 Storage

Metreleptin should be stored according to the current USPI.

9.5 Compliance

The administration of metreleptin (dose and duration) should be recorded in the appropriate sections of the Case Report Form.

Information regarding the patient's prescription renewal will be used to support treatment compliance.

9.6 Accountability

Study drug will not be provided.

9.7 Concomitant and Other Treatments

Patients receiving immunomodulatory drugs should not be enrolled in this study (refer to Section 4.4).

9.7.1 Other Concomitant Treatment

Unless excluded (Section 4.4), medication considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator and should recorded in the appropriate sections of the eCRF. Special attention should be paid to recording changes to the patient's anti-diabetic of lipid lowering treatments as these modifications may affect efficacy determination.

10. STATISTICAL ANALYSES

10.1 Statistical Considerations

Analyses will be performed by Aegerion or designee.

A comprehensive Statistical Analysis Plan will be prepared and finalized before database lock.

10.2 Sample Size Estimate

Ten patients who have been prescribed metreleptin for generalized lipodystrophy will be included in this study; patients will be evaluated for a period of 3 years.

Pooled data from 2 previous studies of metreleptin for lipodystrophy (NIH 991265/20010769 and FHA101 [NCT00677313, FHA101]) indicated the proportion of patients who developed binding antibodies to metreleptin at titers ≥25 was 80% after treatment with metreleptin. If 10 patients are enrolled in this study, there is 87.9%

certainty that a minimum of 6 out of the 10 patients will have a titer of binding antibody ≥25. The expected distribution of maximum titer for these 10 patients is presented in 5.

Table 5: Expected Number of Patients with Maximum Antibody Titer

MAXIMUM TITER	NUMBER OF PATIENTS
0	1
5	1
25	1
125	2
625	3
3125	2
15625	0

Studying 10 patients in this rare population is adequate to confirm previous immunogenicity results from both the obesity and lipodystrophy development programs. Following patients for 3 years should be adequate to assess time to peak titer since previous data suggest a range of 4 to 7 months. *In vitro* neutralizing activity will also be measured in all antibody positive samples, and may be detected by either the receptor cell-based assay or the ligand-binding assay (under development). However, if 0 out of 10 enrolled patients is observed with *in vitro* neutralizing activity, the point estimate (90% confidence interval) for the proportion of patients with neutralizing activity is 0.00 (0.00, 0.26) (computed in StatXact version 7.0). Because generalized lipodystrophy is a rare disease and events of *in vitro* neutralizing activity are infrequent, it is not feasible to gain a precise estimate of *in vitro* neutralizing activity; this study is not designed to determine this estimate.

10.3 Definitions of Analysis Sets

The following will be used for all analyses:

- Patients treated with at least one dose of metreleptin will be included in the assessment of safety and tolerability.
- Patients treated with a dose of metreleptin and with baseline and postdose efficacy data will be included in the assessment of immunogenicity and efficacy analyses.

10.4 Outcome Measures for Analyses

Anti-metreleptin, anti-HuL percent inhibition and binding antibody titers, and category of *in vitro* neutralizing activity to metreleptin in the cell-based assay will be used to assess immunogenicity. Antibody samples will be tested for *in vitro* neutralizing activity using the newly developed receptor-binding assay for metreleptin and cell-based assay methods.

HbA1c and fasting triglycerides will be used to assess efficacy.

Serious adverse events, AESIs, AEs leading to discontinuation, vital signs, clinical chemistry, hematology, and urinalysis data will be used to assess safety and tolerability.

The following outcome will be measured:

- Maximum of antibody titer (anti-metreleptin, anti-HuL) by visit
- Percent inhibition of metreleptin and leptin by visit

10.5 Methods for Statistical Analyses

There will be no hypothesis testing. All data will be summarized by descriptive statistics and/or listings. In general, continuous variables will be summarized by n, mean, SD, median, min and max. Number of patients and percentage of patients in a category will be provided.

Descriptive statistics will be provided for immunogenicity variables (Section 10.4). The maximum antibody titer (anti-metreleptin or anti-HuL) during a visit will be summarized by visit. Categorization of *in vitro* neutralizing activity as assessed by cell- based assay will be summarized across visits; the rate of Category D and E *in vitro* neutralizing activity with 90% and 80% exact confidence intervals will be computed. The results are reported as percent inhibition and 80% inhibition is currently utilized as the neutralizing antibody threshold. activity Results for *in vitro* neutralizing activity will be summarized across visits; however, there will be no formal comparison of the 2 assay methods for the detection and relative potency of Category D or E *in vitro* neutralizing activity.

Maximum antibody titers, neutralizing activities detected by both methods, and metreleptin exposure for each patient will be plotted over time. Maximum antibody

titers, neutralizing activities detected by both methods, and any associated clinical events (i.e., loss of efficacy or AE) will be summarized.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients who experienced at least 1 AE will be summarized by system organ class and preferred term. AEs will be summarized by relationship to the study medication and by severity. Deaths, SAEs, AESIs, and AEs leading to discontinuation will be tabulated and/or listed. SAEs, AESIs and AEs leading to discontinuation will be summarized respectively by peak antibody titers (anti-metreleptin, anti-HuL) and by *in vitro* neutralizing activity categories or percent inhibition.

Clinical laboratory results (hematology, chemistry, and urinalysis), and vital signs results will be summarized using descriptive statistics for each visit.

Change from baseline in HbA1c and percent change from baseline in fasting triglycerides will be summarized for each visit by overall patient population, by peak antibody titers (anti-metreleptin, anti HuL), and by *in vitro* neutralizing activity categories or percent inhibition , respectively.

11. STUDY AND DATA MANAGEMENT

11.1 Training of Study Site Personnel

Before the first patient is entered into the study, an Aegerion representative or designee will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and the EDC system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

11.2 Monitoring of the Study

During the study, an Aegerion representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The Aegerion representative or designee will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

11.2.1 Source Data

Source data will be stored at the individual study sites.

11.2.2 Study Agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between Aegerion and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

11.2.3 Archiving of Study Documents

The Investigator follows the principles outlined in the CSA.

11.3 Study Timetable and End of Study

The end of the study is defined as 'the last visit of the last patient undergoing the study.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. Aegerion may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with metreleptin.

11.4 Data Management

Data management will be performed by Aegerion or designee. Serious adverse events and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the WHO Drug Dictionary. Classification coding will be performed by Aegerion or designee.

Any data collected through third-party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

11.4.1 Serious Adverse Event Reconciliation

Serious adverse event and AESI reconciliation reports are produced and reconciled with the Drug Safety database and/or the investigational site.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/GCP and applicable regulatory requirements.

12.2 Patient Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

12.3 Ethics and Regulatory Review

An Institutional Review Board (IRB) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable IRB, and to the study site staff.

The opinion of the IRB should be given in writing. The Investigator should submit the written approval to Aegerion or designee before enrollment of any patient into the study.

Aegerion or designee should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, will be approved by the national regulatory authority or a notification to the national regulatory authority will be completed, according to local regulations.

Aegerion or designee will handle the distribution of any of these documents to the national regulatory authorities.

Aegerion will provide regulatory authorities, IRBs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. Aegerion will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

12.4 Informed Consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that he/she is free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the patient.
- Ensure that any incentives for patients who participate in the study, as well as any provisions for patients harmed as a consequence of study participation, are described in the ICF that is approved by an Ethics Committee.

12.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of coordinating Investigator and Aegerion.

If there are any substantial changes to this study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant IRB and, if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

Aegerion will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRBs, see Section 12.3.

If a protocol amendment requires a change to a center's ICF, Aegerion and the center's IRB are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to, or approved by, each IRB.

12.6 Audits and Inspections

Authorized representatives of Aegerion, a regulatory authority, or an IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact Aegerion immediately if contacted by a regulatory agency about an inspection at the center.

12.7 Registration of the Trial

This trial will be registered in an appropriate clinical trial database before initiation (e.g., www.clinicaltrials.gov), in accordance with regulations in the countries involved in study conduct. Any results (including negative findings) will be published or otherwise made available to all researchers and the public in accordance with regulations.

12.8 Disclosure

The PI certifies that all conflicts of interest will be disclosed in writing to the Sponsor. Conflict of interest is defined as a situation in which financial or other personal considerations have the potential to compromise or bias professional judgment or objectivity.

12.9 Data Quality Assurance

The Sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, the Sponsor or Sponsor's designee

personnel and the PI will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study, and eCRFs will be verified against source documents. The Sponsor Medical Monitor will review the data for safety information. Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

12.10 Final Study Report

An integrated clinical and safety report will be prepared at the conclusion of the study. The interim and final reports will be in accordance with the ICH E3 Guideline for Industry: Structure and Content of Clinical Study Reports.

If applicable, agreement with the final Clinical Study Reports will be documented by the dated signature of the Coordinating Investigator(s), in compliance with Directive 75/318/EC, Directive 2001/83/EC, and ICH E3. The Coordinating Investigator(s) will be selected prior to database lock based on criteria such as: country requirements for identification of a Coordinating Investigator and enrollment status.

12.11 Insurance

Aegerion has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the study protocol as well as with applicable laws and standards.

12.12 Publication Policy

The Sponsor holds all publication rights to the data obtained from this study. Before any data from this study are published on the initiative of an investigator, a manuscript will be

sent to the Sponsor for review and approval at least 30 days prior to submission to the publisher.

12.13 Study Records and Source Documents

During the trial and after termination of the trial, including after early termination of a trial, the PI must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, eCRFs and other data collection forms (e.g., screening forms, including those for screen failures), advertising for patient participation, AE reports, patient source data, correspondence with health authorities and IRBs/IECs, consent forms, PI's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The Sponsor must be consulted if the PI wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The PI must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines.

- ICH E6 Guidance specifies that records must be retained for a minimum of two years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.

All trial documents shall be made available if required by relevant health authorities. The PI should consult with the Sponsor prior to discarding trial and/or patient files.

The Sponsor will retain all Sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that back-up exists and that a paper copy can be obtained from it, if required.

To maintain confidentiality, the patients will be identified by numbers and/or initials on the eCRFs. Electronic CRFs for patients who fail screening must also be retained.

The Sponsor reserves the right to terminate a study site for refusal of the PI to supply source documentation of work performed in this clinical study.

12.14 Confidentiality

All unpublished information that the Sponsor gives to the PI shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The PI shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the Clinical Study Agreement.

13. LIST OF REFERENCES

1. MYALEPT Prescribing Information

   Myalept (metreleptin). U.S. Prescribing Information. Available from URL: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c986f93b-855d-4ef0-b620-5d41a0513e48 (Accessed 07Sep2016)

2. Investigator's Brochure for Metreleptin

   Metreleptin (Recombinant-methionyl Human Leptin) [Investigator's Brochure]. Refer to current version.

3. NCT00677313, FHA101

   ClinicalTrials.gov. An open-label treatment protocol to provide metreleptin for the treatment of diabetes mellitus and/or hypertriglyceridemia associated with lipodystrophy. https:// https://clinicaltrials.gov/ct2/show/NCT00677313?term=FHA101&rank=2 (Accessed 08Nov2016).

APPENDICES

Appendix A: Additional Safety Information

Appendix B: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Appendix A: Additional Safety Information

Appendix B: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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1. FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

1.1 Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

1.2 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

1.3 Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm

- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

2. A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Aegerion would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

A 36-Month, Multicenter, Open Label Phase 4 Study to Evaluate the Immunogenicity of Daily SC Metreleptin Treatment in Patients with Generalized Lipodystrophy

Protocol AEGR-734-401

Appendix B: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

08 February 2018

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1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Aegerion clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3x ULN **together with** TBL ≥2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3xULN
- AST ≥3xULN
- TBL ≥2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to Aegerion representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the Aegerion representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Aegerion representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the Aegerion representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6)
- Notify the Aegerion representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Aegerion Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the Aegerion standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Aegerion standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
    - If there is no significant change no action is required
    - If there is a significant change notify the Aegerion representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6?

If No: Follow the process described in Section 4.2 of this Appendix

If Yes: Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation': Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf