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For patients studied using grant funds from 5RO1-DK 088114A1-02

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CLINICAL PROTOCOL to investigate the long-term safety and efficacy of recombinant human leptin (METRELEPTIN) in various forms of Partial Lipodystrophy

For patients studied using grant funds from 5RO1-DK 088114A1-02

Investigators:

Elif Arioglu Oral, MD[1] (Principle Investigator)
Hari Conjeevaram, MD, MPH[4]
Charles Burant MD, PhD[1]
Nevin Ajluni, MD[1]
Thomas Chenevert, PhD[2]
Adam Neidert, MS[1] (coordinator)

1. Department of Internal Medicine, Metabolism, Endocrine and Diabetes, Division, University of Michigan, Ann Arbor, Michigan
2. Department of Radiology, University of Michigan, Ann Arbor, Michigan
3. Department of Pathology, University of Michigan, Ann Arbor, Michigan
4. Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

Contact Address:
Elif Arioglu Oral, MD
Brehm Center for Diabetes Research
Fifth floor, room 5313, Brehm Tower
1000 Wall Street, Ann Arbor, MI 48105

eliforal@umich.edu
phone: (734) 615-7271
fax: (734) 232-8162

Investigational Drug:
Metreleptin (AC164594)
Provided by: Amryt
IND Number 72,734

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TABLE OF CONTENTS

1. SPECIFIC AIMS FOR THE PROTOCOL:

Leptin is now an approved therapeutic in the form of Myalept in patients with generalized forms of lipodystrophy. However, it is still under investigation for patients with partial forms of the disease based on FDA decision on February 24, 2014. We have been conducting the clinical research protocol: "CLINICAL PROTOCOL to investigate the efficacy of recombinant human leptin (METRELEPTIN) in nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) associated with lipodystrophy (MB002-014)" under IND 72,734. All of patients enrolled on this ongoing protocol have partial lipodystrophy, specifically familial partial lipodystrophy.

We would like to create this novel protocol to allow continued treatment of patients with partial forms of lipodystrophy who volunteered and completed treatment under our ongoing protocols and who have derived significant clinical benefit as judged by an amelioration of their HbA1c, triglyceride levels, and/or reduction in their baseline diabetes or lipid therapies that affect quality of life.

Therefore, our aim is to determine the long term safety and efficacy of Metreleptin (Myalept,) in promoting amelioration of metabolic abnormalities in patients with all forms of partial lipodystrophy. Patients who have completed University of Michigan research protocol MB002-014 and have shown improved clinical benefit as judged by clinical criteria set forth in this protocol will be offered the opportunity to participate in this new research study.

The primary outcome measure will be percent change in fasting triglyceride levels. The hypothesis is that the triglyceride levels will not change during the follow up period. Secondary outcome measure will be percent change in HbA1c values again with the hypothesis that this will not change during the follow up period.

Exploratory outcomes:
We will measure change in liver function tests, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). We will also explore body weight, body composition, free fatty acid levels, and HOMA-IR.

2. PROTOCOL:

Study goal: We now would like to continue observation in patients who have exhibited significant clinical benefit who have demonstrated a significant clinical benefit and for whom other therapies have previously failed to provide adequate control in the absence of metreleptin. In order to accomplish this aim, we now propose an open-label prospective continued long-term study with recombinant human leptin therapy *in patients with all forms of partial lipodystrophy. The goal of this study is to allow treatment of patients for long term and this study is designed more like an expanded access intention.*

2.1 STUDY DESIGN

Screening information: Patients will be evaluated at the time of completion of the parent study.

2.2 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria for initial phase of the study:

- Previously completed study protocol:
  - CLINICAL PROTOCOL to investigate the efficacy of recombinant human leptin (METRELEPTIN) in nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) associated with lipodystrophy, MB002-014 (IRMBED: HUM00058708)
- Demonstrates clinical benefit as defined by meeting at least one of the following criteria upon completion of the above stated protocols:
  - Reduction of HbA1c ≥ 1.0% or,
  - Reduction of triglycerides ≥ 30% of baseline or,
  - Decrease in insulin requirements ≥ 40% or,
  - Reduction in total NASH score by ≥ 2 points,
  - Significant worsening of metabolic parameters after discontinuation of Metreleptin if discontinuation has been undertaken.
  - A health condition that appears to have significantly improved by metreleptin for which two independent health care providers make a request to prevent drug discontinuation. In addition, the PI has to document absence of contraindications for drug continuation (such as bone marrow suppression).
- Is male or female ≥ 5 years old at baseline.
- Is male, female not of childbearing potential, or meets all the following criteria if female of childbearing potential (including perimenopausal women who have had a menstrual period within one year):
  - Not breastfeeding
  - Negative pregnancy test result (human chorionic gonadotropin, beta subunit [βhCG]) at baseline (not applicable to hysterectomized females).
  - Must practice and be willing to continue to practice appropriate birth control (defined as a method which results in a low failure rate when use consistently and correctly, such as implants, injectables, oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, tubal ligation, or a vasectomized partner) during the entire duration of metreleptin treatment.
- Has physician-confirmed lipodystrophy as defined by evidence of partial (limbs) loss of body fat outside the range of normal variation.
- If ≥ 18 years of age, is able to read, understand and sign the U of M IRBMED approved informed consent form (ICF), communicate with study physician and study team, understand and comply with protocol requirements.
- If < 18 and ≥ 7 years of age, is able to read, understand and sign the appropriate U of M IRBMED approved assent form and has a parent or legal guardian that is able to read, understand and sign the ICF.
- If < 7 and ≥ 5 years of age or unable to read, the appropriate assent form must be explained to the child.
- If previously treated with thiazolidinediones or Vitamin E, stable dose of these medications for at least 3 months.

Exclusion criteria:

- Presence of advanced liver disease (as evidenced by abnormal synthetic function, abnormal PT or albumin).
- Evidence of other etiologies of viral hepatitis.
- Presence of clinically significant hematologic abnormalities (such as neutropenia and/or lymphadenopathy).
- Presence of HIV infection.
- Inability to give informed consent.
- Presence of ESRD, any type of active cancer, or >class 2 congestive heart failure ((New York Heart Association Functional Classification System), based on medical history and physical examination.

Study Inclusion:

Criteria for continuation into the long-term phase is based solely on proven clinical benefit using criteria universally accepted to be beneficial. The following criteria are accepted as evidence of substantial clinical benefit upon completion of CLINICAL PROTOCOL to investigate the efficacy of recombinant human leptin (METRELEPTIN) in nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) associated with lipodystrophy, MB002-014 (IRMBED: HUM00058708):

- Reduction of HbA1c ≥1.0% or,
- Reduction of triglycerides ≥30% of baseline or,
- Decrease in insulin requirements ≥40% or,
- Reduction in total NASH score by ≥2 points.
- Significant worsening of metabolic parameters after discontinuation of Metreleptin if discontinuation has been undertaken.

- A health condition that appears to have significantly improved by metreleptin for which two independent health care providers make a request to prevent drug discontinuation. In addition, the PI has to document absence of contraindications for drug continuation (such as bone marrow suppression).

Study group: We will enroll up to a total of up to 15 subjects to receive study drug Metreleptin from our parent studies.

Restorative leptin therapy: This is defined as administration of recombinant methionyl-human leptin subcutaneously to achieve high normal levels of circulating leptin in individuals who started out with lower than normal or low normal levels of circulating leptin(1, 2). Recombinant human leptin will be provided by Amryt Pharma (Boston, MA). Previous experience from patients with lipodystrophy or with congenital absence of leptin indicates that this goal can be achieved by administration of 0.02 to 0.10 mg/kg/day in adult males depending on baseline leptin concentrations and body surface area of the patients. In this study, patients will be treated with 2.5 and 5 mg /day (male and female respectively) to achieve high physiological concentrations. Higher dose titrations can be used in the judgment of the PI as indicated up to 10 mg daily. It is important to note that the patients enrolling in this long term study will be on metreleptin therapy that has been found effective, therefore, their dose will likely not change during this protocol. .

Treatment: Up to fifteen patients will be enrolled into this long-term treatment extension study. Patients will be continued on metreleptin treatment as mentioned. This will be injected subcutaneously after reconstitution once a day in the morning at approximately the same time of the day that fits the subject's calendar. Dose may be titrated up to 15 mg daily based on metabolic response as needed.

Follow-up schedule and monitoring: Scheduled outpatient visits will occur at 6 month intervals. Tolerability will be assessed at each visit. During each visit, patients', weights, BMI, injection site inspection and basic laboratory data (comprehensive metabolic panel (fasting glucose, BUN, creatinine, sodium, potassium, chloride, CO_2, calcium, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase), fasting insulin, fasting leptin levels, fasting lipid panel (total cholesterol, triglycerides, HDL, LDL)), will be recorded. Throughout the study, lab work for CBC with differential count and creatinine kinase will be obtained at each visit.

Unscheduled visits may occur at more frequently than ever six months in order to follow-up on any adverse event or unanticipated health issues participants may be having.

Study Termination: Patient participation will be concluded five years after the patient's baseline appointment. At this time normal follow-up study procedures will be conducted, final drug accountability will be performed and patient will be transitioned to clinical care.

Preparation for study visits: Subjects will be asked to refrain from alcohol or tobacco use for 72 hours prior to the visit. They will report to the Research Center after 10 hours of fasting. They will be allowed to consume water overnight prior to the studies.

2.3 EVALUATION OF PROCEDURES OF THE STUDY

A. Metabolic evaluation of lipodystrophic patients with NASH or NAFLD (tests will be conducted after a 10 hour fast, will be done at each visit).

1. Blood Chemistry: The following tests will be performed after an overnight fast: fasting glucose and insulin, fasting triglyceride levels, hemoglobin A1c, fasting free fatty acid levels, fasting total, HDL and LDL cholesterol, serum ALT, AST, albumin, alkaline phosphatase, bilirubin (direct and indirect), serum electrolytes, BUN and creatinine, calcium. The previously listed blood chemistry tests will be charged to the patient's insurance as standard, routine care procedures. Approximately 10cc of serum will be aliquoted and frozen for potential future tests.

2. Determination of insulin sensitivity using HOMA-IR: The homeostatic model assessment (HOMA) will be used as a surrogate estimate of insulin resistance based on fasting insulin and glucose concentrations and calculated as fasting insulin concentration (mU/L) x fasting glucose concentration (mmol/L)/22.5 (5).

B. Research sample

We will also collect and store samples for determination of TNF-α soluble receptor, TGF-B, FGF-21 and other potential markers.

2.4 EXPECTED RESULTS

We anticipate collecting safety and efficacy data for long-term treatment of patients with partial forms of lipodystrophy.

3. STUDY DRUG:

Other Names: MyaLept (Recombinant-methionyl Human Leptin (r-metHuLeptin) METRELEPTIN)

3.1 STORAGE CONDITIONS AND STABILITY

The study drug will be stored in a secure location under controlled conditions at the study site or pharmacy before dispensing to subjects. Metreleptin will be stored at 2-8° C prior to reconstitution. It is recommended that the refrigerator be connected to a back-up power source, and a temperature alert system**. Amryt** will be notified if any test material is exposed to excessive or uncontrolled temperatures; possible replacement of the affected material will be considered. Study staff and subjects will be instructed in proper storage of the study drug.

3.2 EXPRIATION DATING

As per standard practice for experimental biologic pharmaceuticals, Amryt Pharma will conduct periodic stability assays to monitor product stability and determine appropriate expiration dating of the study drug. The appropriate **Amryt** representative shall communicate this information to the investigator**.**

Amryt representative: Will Fallon
Sr. Supply Chain Manager
Amryt Pharma PLC
Telephone: +353 1 518 0235

3.3 DRUG DOSAGE AND ADMINISTRATION

Metreleptin will be administered by subcutaneous injection at the doses specified above. Subjects will be instructed by study personnel to reconstitute the medication and self-administer the injections and will perform the first injection under the supervision of study personnel.

The dosing recommendations for Metreleptin are listed below:

Body Weight	Gender	Daily Recommended Metreleptin Dose
≤40 kg	Male	0.06 mg/kg
	Female	
>40 kg	Male	2.5 mg (0.5 mL)
	Female	5.0 mg (1.0 mL)

Initial Metreleptin dose may be adjusted based upon the subject's dose at termination of the two previous studies for reasons of efficacy. Metreleptin dose may be adjusted at investigator's discretion based on clinical response (e.g. inadequate metabolic control or excessive weight loss or tolerability issues). Injections at a single site will have a maximum allowable volume of 2.0 ml. Preferably study medication will be administered at approximately the same time each day. Drug administration will occur once a day (QD). Metreleptin administration may be changed to twice a day (BID) at investigator's discretion based on clinical response (e.g. inadequate metabolic

control, tolerability issues). Dose exceeding 1.0 mL may be administered as two separate injections in order to minimize patient discomfort due to injection volume. Metreleptin dose can be injected into the abdomen, upper arm or thigh region depending on patient preference and comfort. The site(s) of injection will not occur on the limb from which subsequent blood draws will occur that day.

3.4 STUDY DRUG PREPARATION

Each single use 5 mL vial of lyophilized Metreleptin (11.3 mg/vial) will be reconstituted with either bacteriostatic or sterile water immediately prior to injection. To reconstitute, 2.2 mL of either bacteriostatic or sterile water will be injected slowly down the inside wall of the vial using a syringe and needle. The vial should be inverted and gently swirled until the powder is completely dissolved. The vial is not to be shaken vigorously. The solution of reconstituted Metreleptin should be clear, colorless, and free of any floating particles. The mixed vial can be used for a maximum of three days or until sufficient volume is left for another full dose**.** As lyophilized Metreleptin contains no preservative, vials are designed for single use only. Latex-free syringes will be used for all procedures with the study drug. Once the vial has been reconstituted, the drug will be administered immediately (no more than 3 hours after reconstitution), as is our current practice. In the lifetime of the study, the manufacturer has conducted studies that indicate safety of use up to 3 days. Given that minimal amounts are left in the vial in our patients and that we had originally instructed them not to reuse the vials, we have been continuing this practice. Before injection, study medication will be allowed to reach room temperature (15 to 30°C). Any solution remaining in the vial can be used for a maximum of three days after reconstitution. Subjects will return all vials to study personnel at the next study visit.

3.5 AVAILABILITY

MyaLept (Metreleptin) is being supplied by Amryt Pharma PLC.

3.6 INITIAL DRUG SHIPMENT AND RE-SUPPLY

A signed and completed Drug Request Form must be faxed, at least **10 days** prior to the expected delivery date, to **the Medical Affairs Representative**. Used as well as unused vials of expired Metreleptin should be destroyed at the site. We will provide copies of copies of all drug tracking and reconciliation logs as well as proof of destruction at the end of the study to Amryt Pharma.

4. POTENTIAL RISKS WITH THE STUDY:

The overall risks of the study can be divided into risks associated with the evaluation methods and risks associated with recombinant leptin therapy. These risks are balanced against the potential benefits of therapy to participants and the knowledge gained from the study.

4.1 RISK ASSOCIATED WITH EVALUATION METHODS

Risks with blood tests: The total amount of blood drawn from the patients will be kept within the IRB restrictions. Total amount of blood to be drawn with the outlined studies is estimated not to exceed 960 cc over the course of 12 months. Each blood draw is associated with pain and risks of infection though these risks are minimal.

Risks with study procedures: In this study, patients are asked to have 2 extensive visits in 12 months. In addition to the above risks some patients may find the time needed to complete the research studies an inconvenience in their routine lives. Each participant into the study will clearly understand that participation is totally voluntary.

Our research plans will be monitored by the University of Michigan IRB.

4.2 RISKS ASSOCIATED WITH TREATMENT WITH RECOMBINANT HUMAN LEPTIN

General: Hypoglycemia was the most frequent treatment-emergent adverse event reported in two previous clinical studies in 29 subjects with lipodystrophy. Metreleptin has been shown to have an antidiabetic effect in lipodystrophic patients. The investigators will monitor subjects with diabetes and consider adjustments to

antidiabetic medications (including insulin), based on the degree of glucose control achieved with the addition of metreleptin to pre-existing diabetic therapy.

In clinical weight loss studies investigating the use of metreleptin in obese patients, injection site reactions were the most common adverse event (erythema, pruritus, inflammation, urticaria and edema). All sites of injection (abdomen, arm and leg) used for the site of injection were affected. Other adverse events mentioned in the Investigator's Brochure are headache, fatigue and flu-like symptoms, weight loss, alopecia and nausea. All these effects occurred with no relationship to dosing.

Two subjects receiving Metreleptin for acquired generalized lipodystrophy developed peripheral T-cell lymphoma. Both subjects had clinically significant hematologic (i.e., neutropenia, pancytopenia, lymphadenopathy), bone marrow, and/or other abnormalities (i.e., hepatosplenomegaly, skin lesions) prior to being started on metreleptin therapy. The evolution of the clinical presentation and eventual diagnosis of peripheral T-cell lymphoma while on metreleptin treatment in these subjects could be consistent with the indolent nature and natural history of this condition, which is often difficult to diagnose. In particular, both patients had clearly abnormal bone marrow biopsies prior to initiating Metreleptin treatment with pathology demonstrating that some form of the disease was already present, at least in the early stages. Similarly, skin lesions similar to those later biopsied and leading to the diagnosis of peripheral T-cell lymphoma were present in one of the patients before metreleptin therapy was started. Moreover, both patients likely had increased risk for developing lymphoproliferative disorders based on their diagnosis of acquired generalized lipodystrophy, a form of lipodystrophy frequently associated with autoimmune diseases. Based on the available information for these two cases of peripheral T-cell lymphoma, it is **the manufacturere's** assessment that there is no evidence that Metreleptin treatment increases the risk of *de novo* development of peripheral T-cell lymphoma, although they do not exclude the possibility that Metreleptin may have contributed to the progression of the lymphoma in these subjects who had clinically significant hematologic abnormalities at baseline. It is also possible that the evolution of the clinical presentation and eventual diagnosis of T-cell lymphoma in these subjects could be consistent with the natural history of the condition.

An additional subject with acquired generalized lipodystrophy was diagnosed with anaplastic large cell lymphoma while on metreleptin treatment in an open-label, ongoing protocol. This subject had no pre-existing history of autoimmune disease or hematological abnormalities. She presented after nearly 2 years of metreleptin treatment with a mass around her right breast that was found to be a lymph node on imaging and was initially treated with antibiotics for a presumptive diagnosis of lymphadenitis. Needle biopsy of the mass showed an anaplastic large cell lymphoma staining positive for ALK (anaplastic lymphoma kinase) and CD30+ (indicating T-cell lymphoma). Additional investigation including PET scan indicated that the lymphoma was highly localized with no evidence of disease elsewhere and minimal enhancement of the primary lesion. Excisional biopsy of the mass was performed and pathology results confirm the diagnosis of anaplastic large cell lymphoma.

Based on current information, the initial assessment of this recent report with specific ALK staining indicates that this anaplastic lymphoma is distinct from the two previous cases of peripheral T-cell lymphoma, which had evidence of pre-existing bone marrow abnormality and skin manifestations. The investigator and Sponsor have assessed this case as possibly related to Metreleptin treatment.

Lab values: With the studies conducted so far, there have been no consistent patterns of changes noted in hematological parameters, ALT, AST, BUN, albumin and CPK values.

Antibodies to Metreleptin: Development of antibodies was noted in 30% of subjects at higher dose levels, comparable to be given in this study (Investigator's Brochure). The antibodies were non-neutralizing, and did not appear to be clinically significant (Investigator's Brochure). Previously, three subjects in a study investigating the use of a pramlintide + metreleptin combination drug therapy for the treatment of obesity in non-lipodystrophic patients (DFA102) did develop neutralizing antibodies. The first two subjects had developed high titer of binding-antibodies to metreleptin, plasma leptin concentrations near or below the lower limit of the assay sensitivity, and neutralizing antibodies at the end of the 28-week study. There were no clear

factors as to why these two particular subjects developed neutralizing antibodies. A third subject currently under investigation appears to have developed the neutralizing antibody after the study termination. It is common for patients receiving peptide therapeutics to develop antibodies against the treatment. Serum samples from 22 lipodystrophic patients, whose metreleptin exposure ranged from 3 months to 27 months, in a different research study using metreleptin in lipodystrophic patients (FHA101, MB002-002) have been tested for neutralizing antibodies. None of these patients' samples showed evidence of developing neutralizing antibodies at the time of the submission to the FDA.

It is our expectation that the assay for neutralizing antibody may change and our understanding of this phenomenon may evolve during the course of the study.

Serum will be saved from each visit to determine the levels of antibodies to Metreleptin. These assays are available through **Amryt.** The antibody assays will be run at yearly intervals after enrollment of the 6th patient. However, serum leptin levels can be used as a surrogate for the development of worrisome neutralizing activity since serum leptin level became undetectable in the two patients in whom neutralizing activity was demonstrated.

4.3 ADEQUACY OF PROTECTION FROM RISKS

A) Recruitment and Informed Consent Procedures. Informed consent will be obtained from study patients by a member of the research team during the baseline visit prior to the initiation of the study protocol. This will be a face-to-face session with the patient and adequate time will be spent to go over the study and to answer the questions. If potential patients so desire, we will provide then with a copy of the current IRB approved consent and assent documents in advance of the baseline visit, either by mail, email or fax. Recruitment procedures and waiver of HIPAA rules for research recruitment will be overseen and approved by University of Michigan's IRB overseeing the research study.

B) Protection Against Risk

Care will be taken to protect the patient from any untoward risks through the entire study period. Patients' privacy will be protected based on HIPAA rules. Recruitment procedures and waiver of HIPAA rules for research recruitment will be overseen and approved by University of Michigan's IRB overseeing the research study. Informed consent documents contain detailed information on personal information of subjects and how these will be protected.

IRB application. This study protocol will be submitted to the University of Michigan IRBMED for initial approval. No patient recruitment, study activity, or any other activity with potential patients will be conducted until the study is approved by the IRBMED. The IND for use of Metreleptin for the purpose of this study is filed with the FDA with number 72,734.

4.4 EARLY SUBJECT DISCONTINUATION

Subjects may be removed from the study prior to completion for the following reasons:

1. Withdrawal of Consent: Subject wishes to exercise the right to withdraw from the study as stated in the ICF (all subjects reserve the right to withdraw from the study without prejudice).
2. Adverse Event: Subject experiences an AE that, in the investigator's opinion, necessitates withdrawal from the study.
3. Investigator Decision: Investigator feels it is in the subject's best interest to terminate participation for reasons other than an AE.
4. Protocol Violation: Subject is noncompliant with protocol procedures, becomes pregnant, violates study entry criteria, or starts an unacceptable concomitant medication.
5. Lost to Follow Up: Subject fails to return for study visits and cannot be reached with reasonable, repeated attempts.
6. Administrative Reason: The FDA or University of Michigan IRBMED regulatory authority discontinues the study protocol or the clinical study site discontinues participation.

5. MONITORING FOR SIDE-EFFECTS AND ADVERSE EVENTS:

Subjects will be screened for occurrence of side-effects at each visit. The laboratory data will be monitored by the study team as well as anonymously presented to an independent Study Monitor.

5.1 ADVERSE EVENTS DEFINITION

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product (ICH Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Federal Register May 9, 1997).

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

All adverse events reported spontaneously by the subject, as well as those noted by the investigator or study site staff, are to be recorded. In order to avoid vague, ambiguous, or colloquial expressions, the adverse event term should be recorded using standard medical terminology rather than the subject's own words. Every attempt should be made to describe the adverse event in terms of a diagnosis. Whenever the investigator is confident in making a unifying diagnosis, all related signs, symptoms and abnormal test results should be grouped together and recorded as a single adverse event.

All subjects who have adverse events, whether or not the adverse events are considered associated with the use of the study medication, must be monitored until the adverse event resolves, stabilizes, or becomes chronic. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the observation period, until a satisfactory explanation for the adverse event is found or the investigator considers it medically justifiable to terminate follow-up.

All adverse events will be evaluated for intensity and causal relationship with use of the study medication.

The most frequently reported adverse events in studies of Metreleptin AC164594 have been skin reactions (injection site reactions) at the site where the drug is injected. These reactions include bruising, redness, pain, itching, inflammation, swelling, dark spots on skin, and lumps under the skin. Other frequently reported adverse events have been hypoglycemia (reported mainly in patients using insulin), decreased weight, hair loss, headache, fatigue, nausea and influenza-like symptoms. There may be additional risks such as potential allergic reaction to the study drug. There have been less frequent reports of generalized rashes, hives, and in rare instants, swelling of the lips and eyes. Further information on the adverse event profile may be found in the AC164594 Investigator's Brochure.

5.2 DEATHS

All deaths on study must be reported to IRBs overseeing the study, Study Monitor, FDA and Amyrt **(or designee)** within 24 hours of notification of the death. In addition, all deaths within 30 days of last investigational drug dose and/or deaths occurring out to the last formal follow-up observational period, whichever is longer. For all deaths, autopsy reports (if applicable) and relevant medical reports must be sent to Amryt **(or designee)** along with the FDA, and relevant IRBs overseeing the study.

5.3 SERIOUS ADVERSE EVENT (SAE) DEFINITION

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

- results in death

- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 1.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 1.4 for reporting pregnancies.)

NOTE:
The following hospitalizations are not considered SAEs for this research study protocol:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

5.4 SERIOUS ADVERSE EVENT (SAE) COLLECTION AND REPORTING

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to the study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to Amryt (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form or other appropriate forms approved by the responsible regulatory authority (e.g., the applicable MedWatch 3500 or CIOMS form); pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: AegerionsPV@ubc.com
SAE Facsimile Number: 1 877 200 2781

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to Amryt (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe pain); the event itself, however, may be of relatively minor medical significance (such as severe headache). By contrast, the term “serious” is used to describe an event based on an event outcome or actions usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

If an SAE occurs, the investigator should initiate appropriate support procedures. Important medical events that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above or result in urgent investigation may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias. If the adverse event is sufficiently severe in the investigator’s judgment, the subject should be removed from study and a termination assessment performed. The subject should be given appropriate care under medical supervision until symptoms cease.

Unexpected, related SAEs must be reported to the FDA in an expedited manner. (Refer to 21 CFR 312 and ICH E2A for guidance.) The investigator will determine expectedness by referring to the most current version of the Investigator’s Brochure. Adverse events that are deemed serious by the investigator (irrespective of suspected causation) should be reported according to local IRB guidelines. Unexpected and related fatal or life-threatening events are reported to FDA by phone or FAX within 7 calendar days. Written report should be sent to FDA within 15 calendar days for any serious unexpected adverse events for which there is a reasonable possibility that the event may have been caused by study drug(s). Any follow-up information that is significant to the report must also be sent to FDA within 15 calendar days of receipt of the new information. All filed SAEs will also be presented to the Study Monitor.

Since the trial is being conducted under a physician’s IND, **the principal investigator (listed on FDA Form 1572) overseeing the trial conduct is responsible for submitting all IND Safety Reports to the Food and Drug Administration (FDA)** in accordance with 21 CFR 312.32. (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32).

The FDA MedWatch 3500 Form with built-in instructions can be downloaded at: http://www.fda.gov/medwatch/getforms.htm. **Click on “Mandatory Reporting” link.**

Ensure that both the event intensity (mild, moderate, severe) and investigator's causality assessment (unrelated or related) are included in the description of the Adverse Event (box 5) on the FDA 3500A form.

In cases where the investigator learns of the SAE after its occurrence and resolution, the time and circumstances of the event should be recorded. The reporting requirements must still be followed.

In addition, the investigators are also responsible for timely reporting of SAEs occurring at their clinical study site to their local Institutional Review Board (IRB)/Ethics Committee (EC) and/or Central IRB (if applicable).

All adverse events occurring during the study, whether or not attributed to study drug, should be included in the investigator's annual IND report to FDA. A copy of any 7 or 15-day reports sent to FDA related to AC164594 should be sent to Amryt's Safety Department (by Fax or mail) within 24 hours of notification or discovery of the event.

The principle investigator may decide to withdraw a subject from the study due to an adverse event. Likewise, the Study Monitor may decide that a subject will need to be withdrawn. A subject may also voluntarily withdraw from treatment due to what he perceives as an intolerable adverse event. If any of these occur, the subject must undergo an end-of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

5.5 NONSERIOUS ADVERSE EVENT DEFINITION

A nonserious adverse event is an AE not classified as serious.

5.6 NONSERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 1.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

5.7 SPECIAL SITUATION REPORTS

Special situations related to the use of the study medication that are not classified as either serious adverse events or non-serious adverse events shall also be reported to the sponsor. These reports would include the following, regardless of whether or not an associated event occurred:

- Drug exposure and outcomes of use of metreleptin during pregnancy and breastfeeding, including drug exposure shortly prior to or during pregnancy or during lactation
- Lack of efficacy (including cases of incomplete, decreased or delayed drug effect)
- Suspected transmission of an infectious agent
- Overdose
- Underdose
- Off-label and misuse
- Medication errors
- Occupational exposure

5.8 LABORATORY TEST ABNORMALITIES

The following laboratory abnormalities should be captured on the non-serious AE CRF Page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

5.9 PREGNANCY

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.
The investigator must immediately notify the Amryt (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 5.4.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.
If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Amryt (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to Amryt (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 5.4.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.
Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

5.10 OVERDOSE

All occurrences of overdose must be reported as SAEs (see Section 5.4 for reporting details).
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

5.11 OTHER SAFETY CONSIDERATIONS

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6. WOMEN, MINORITY AND CHILDREN INCLUSION IN CLINICAL RESEARCH

1. Inclusion of Women: The use of pregnant women is not the central focus of this research. Pregnancy, women who think they may be pregnant, women who are actively trying to conceive, and women who are currently breast-feeding are exclusion criteria for enrollment in this study. The general informed consent documents will advise sexual abstinence or use of contraception for female participants of child bearing age. The use of metreleptin is intended to provide direct benefit to women participating in this trial. There are no other accepted medical treatments that are likely to provide the same benefit.

2. Inclusion of Minorities: In our study, all patients with physician confirmed lipodystrophy and ultrasound confirmed non-alcoholic fatty liver disease will be recruited regardless of race and ethnicity. We will continue to do every effort to recruit minorities. If the number of minorities seems to be disproportionately low, we will ask for help from the MCRU Minority Recruitment Board**.**

3. Inclusion of Children: Subjects < 5 years old will not be included in this study as they would require a pediatric expertise not available at this study location. Subjects ≥ 5 years old will be included in this study as NAFLD in lipodystrophic patients is a rare disease with no other approved option for treatment. Liver biopsies are considered to be standard of care treatment for lipodystrophic patients and therefore these juvenile patients will not be placed at an unacceptable risk by having two liver biopsies preformed as part of this research study. In this protocol's parent study and **in an ongoing study, FHA101, four pediatric patients have been successfully and safely treated with metreleptin.**

7. DATA SAFETY AND MONITORING PLAN

In order to ensure the safety of our subjects, we have taken the following general precautions:

1. All research project personnel have completed training in the protection of human research participants per DHHS guidelines;
2. Oversight from different regulatory bodies such as IRBMED and MCRU Advisory Council will be obtained prior to initiation of the study.
3. Adverse event (AE) and serious adverse event definitions are included in the protocols. Grading and Attribution Scales are also listed in the protocol as above.
4. A plan for unexpected adverse event (AE) and serious adverse event (SAE) reporting is included in the protocol as above.
5. The following entities will be notified in case of any unexpected AE and SAE: IRBMED, MCRU, MDRTC, National Institutes of Health (NIH) and the FDA.
6. We plan to submit an annual report of all adverse events (AE) to the IRB, MCRU, MDRTC and US NIH.
7. An independent Study Monitor will review safety data for this study. Dr. William Herman has accepted to act as Study Monitor. The Monitor will review anonymous data every year. Patient data will be provided with case numbers. In addition, the Monitor will review all the SAEs. If there is a reason to stop therapy in a particular patient, the Monitor will direct the Principle Investigator. Also, the Monitor may decide to halt this study if there is a pattern of SAEs.

7.1 STUDY MONITORING PLAN

Since the primary investigator also acts as the study sponsor for this clinical research trial, the primary investigator or designee(s) will conduct periodic audits of all research subjects' medical records, laboratory records, source documents, case report forms and informed consent documentation for each patient at the clinical research site. These audits will also review the regulatory submissions for the research trial as well as any other administrative issues that the primary investigator/study sponsor or designee(s) feels warrant inspection for the proper implementation and conduct of the clinical research study.
This monitoring will occur twelve months after the first patient has initiated the protocol, and continue on a yearly basis. Study monitoring will also be conducted on an annual schedule once all study subject activity has been completed for the research trial.

Monitoring of the investigational drug (Metreleptin) will be conducted by the primary investigator/study sponsor or designee(s) during the clinical research trial. This monitoring will occur at the University of Michigan Investigational Pharmacy Services (IDS) located in the University of Michigan Hospital Pharmacy. Investigational drug monitoring will occur at least once every six months while study subjects are receiving study medication. A final investigation drug monitoring will occur once all subjects have completed the protocol and all investigational drug supply has been returned to IDS or otherwise accounted for.

Study monitoring and investigational drug monitoring can occur at a more frequent schedule or for case if the primary investigator/study sponsor deems so necessary. A record of this monitoring will be kept in the study regulatory binder and will be reported to the U of M IRBMED as an ORIO along with the research trial's annual schedule continuing review.

In addition, regulatory agencies may conduct a regulatory inspection. If such an inspection occurs, the primary investigator/study sponsor agrees to notify the University of Michigan IRBMED upon notification by the regulatory agency. The primary investigator/study sponsor agrees to allow the inspector direct access to all relevant documents and to allocate his or her time and that of the protocol-site personnel to the inspector to discuss findings and any relevant issues. The primary investigator/study sponsor will allow University of Michigan IRBMED personnel to be present as an observer during a regulatory inspection, if requested.

REFERENCES FOR PROTOCOL

1. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, et al. Leptin-replacement therapy for lipodystrophy. N Engl J Med. 2002;346(8):570-8.
2. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency [see comments]. N Engl J Med. 1999;341(12):879-84.
3. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313-21.
4. Fowler PA, Fuller MF, Glasbey CA, Cameron GG, Foster MA. Validation of the in vivo measurement of adipose tissue by magnetic resonance imaging of lean and obese pigs. Am J Clin Nutr. 1992;56(1):7-13.
5. Haarbo J, Gotfredsen A, Hassager C, Christiansen C. Validation of body composition by dual energy X-ray absorptiometry (DEXA). Clin Physiol. 1991;11(4):331-41.
6. Dixon JB, Dixon AF, O'Brien PE. Improvements in insulin sensitivity and beta-cell function (HOMA) with weight loss in the severely obese. Homeostatic model assessment. Diabet Med. 2003;20(2):127-34.
7. Sparti A, DeLany JP, de la Bretonne JA, Sander GE, Bray GA. Relationship between resting metabolic rate and the composition of the fat-free mass. Metabolism. 1997;46(10):1225-30.

APPENDIX

Protocol Table 1: Schedule of Study Procedures			
Studies	**Baseline**	**Follow up visits (occurring at six month intervals)**	**Unscheduled visit*** **
Fasting biochemistry	**X**	**X**	**X**
Fasting adipocytokines	**X**	**X**	**X**
Fasting appetite regulators	**X**	**X**	**X**
Leptin sampling	**X**	**X**	**X**
Metabolomics sample	**X**	**X**	**X**
HOMA-IR	**X**	**X**	**X**
Weight, Height, and Vitals	**X**	**X**	**X**
Study medication distribution and accountability	**X**	**X**	**X**
Leptin (mg/kg/day)	*5.0 – 10.0 mg/day*	*5.0 – 10.0 mg/day*	*5.0 – 10.0 mg/day*
****Study procedures may be omitted at investigator's discretion during unscheduled visits.*			