CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125390Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA: 125390	Submission Date(s): 12/15/10; 3/27/2013; 8/27/13
Brand Name	Myalept
Generic Name	Metreleptin; recombinant-methionyl human leptin
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Amylin Pharmaceuticals
Submission Type; Code	Original; Priority
Formulation; Strength(s)	10 mg lyophilized cake for subcutaneous Injection
Proposed Indication	Treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy.
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1 Executive Summary

Metreleptin is a recombinant analog of human leptin indicated for the treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy. Metreleptin is being submitted as a rolling BLA submission per agreement with the Agency. The last module for this application was submitted on March 27, 2013.

Amylin Pharmaceuticals has requested a priority review for the application. The request is based on the unmet medical need for which metreleptin has been granted both Fast Track and Orphan Drug Designation. The pivotal data for this orphan BLA are based on 72 lipodystrophy patients treated with metreleptin in 2 open-label, investigator-sponsored studies (completed Study 991265 and ongoing Study 20010769, integrated into a single analysis) conducted at the NIH in Bethesda, MD (IND 60,534 filed by Dr. Philip Gorden and cross-referenced to the Sponsor IND 50,259).

The Agency granted the request and the application is under Priority review cycle. Advisory Committee Meeting is planned for December 8, 2013 to discuss the efficacy and safety of metreleptin.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 3/27/13 under BLA125390 and find it acceptable. A Required Office Level OCP briefing was held on November 15, 2013. The labeling comments on pages 36-38 should be communicated to the sponsor.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Table 1 summarizes the key pharmacokinetic properties of metreleptin.

Table 1: Highlights of Clinical Pharmacology

<table>
<tr><td>Proposed dose</td><td>
<table>
<tr><td colspan="2">Once daily subcutaneous administration:</td></tr>
<tr><td>Baseline Weight</td><td>Daily Dose</td></tr>
<tr><td>≤40 kg (male & female)</td><td>0.06 mg/kg</td></tr>
<tr><td>>40 kg</td><td></td></tr>
<tr><td>Males</td><td>2.5 mg</td></tr>
<tr><td>Females</td><td>5.0 mg</td></tr>
<tr><td colspan="2">The higher dose in female patients was based upon the observation that in the general population, females have higher physiological concentrations of leptin when compared to males even after adjustment for differences in body composition.</td></tr>
<tr><td colspan="2">Dose adjustment (increments/decrements) based on clinical response (e.g. inadequate metabolic control, excessive weight loss, or tolerability issues):</td></tr>
<tr><td>Baseline Weight</td><td>Dose Adjustment</td></tr>
<tr><td>≤40 kg</td><td>Increments or decrements of +/- 0.02 mg/kg</td></tr>
<tr><td>>40 kg</td><td>Increments or decrements of +/- 1.25 mg to 2.5 mg</td></tr>
</table>
</td></tr>
<tr><td>PK</td><td>• Cmax and AUC0-10h were approximately dose-proportional over the range of SC doses from 0.01 mg/kg to 0.3 mg/kg (healthy subjects)
• No accumulation would be anticipated based on PK in the studied population for subjects that are negative for binding antibody titers to metreleptin. In lipodystrophy patients, accumulation of total leptin (endogenous leptin plus metreleptin) after repeat dosing was observed and this was accompanied by antibody formation to metreleptin.</td></tr>
<tr><td>Absorption</td><td>• Tmax: ~4 h in lipodystrophy patients</td></tr>
<tr><td>Distribution</td><td>• No protein binding studies were conducted.
• Vd/f or Vd in healthy:
<table>
<tr><td>Dose (mg/kg/day)</td><td>V_z (mL/kg)</td></tr>
<tr><td></td><td>Mean ± SD</td></tr>
<tr><td>0.3</td><td>370 ± 184</td></tr>
<tr><td>1.0</td><td>398 ± 92</td></tr>
<tr><td>3.0</td><td>463 ± 116</td></tr>
</table>
</td></tr>
<tr><td>Metabolism</td><td>• Eliminated by catabolism.</td></tr>
</table>

Elimination	• Renal clearance followed by degradation in the renal tubules. • Following IV injections, half-life was 3.3 h to 3.4 h for doses ranging from 0.3 mg/kg/day to 3.0 mg/kg/day in healthy subjects negative for antibodies to metreleptin. • Although not verified, subjects positive for antibodies to metreleptin exhibit a longer terminal t1/2, presumably due to a reduction in renal elimination. • CL following IV injections was 80 mL/h/kg to 96 mL/h/kg for doses ranging from 0.3 mg/kg/day to 3.0 mg/kg/day in healthy subjects
Intrinsic/ Extrinsic Factors	• Effect of age, gender, race, hepatic and renal impairment on PK has not been studied. • DDI studies with metreleptin have not been conducted.

Dosing:

Dosing of metreleptin was empirical and evolved as the investigators gained experience in the NIH trials. Weight based dosing was initially used which was changed to a fixed dosing. Based on data from NIH pivotal studies 991265/20010769, Amylin has proposed a fixed metreleptin dosing regimen (total daily dose of 5 mg in females and 2.5 mg in males) for patients >40 kg. The difference in gender in leptin levels is also supported by literature data. A weight-based dosing is proposed for patients with weight <40 kg (total daily dose of mg/kg), which is intended to capture the majority of pediatric patients.

Dosing of metreleptin evolved over time from a BID to a QD dosing regimen without changes in efficacy. A total of 32 patients in the NIH pivotal studies were initiated on BID dosing and then transitioned to QD dosing, 22 received metreleptin BID only; and 18 received metreleptin QD only. Based on this, a QD approach is proposed. There is limited experience for doses higher than 10 mg per day. Thus sponsor has proposed that the dose should not exceed 10 mg/day.

Immunogenicity:

All patients receiving metreleptin and who had antibody status assessed developed binding antibodies to metreleptin. In the NIH trials, of the 43 patients with antibody data, 37 (86%) developed detectable antibodies following exposure to metreleptin, with peak titers ranging from 1 month to 42 months following initiation of metreleptin for the time points at which samples were analyzed.

Of the 22 patients in FHA101 study who were negative for binding antibodies to metreleptin at baseline, 21 patients developed detectable binding antibodies following exposure to metreleptin. The time to peak titer ranged from 3 months to 18 months following initiation of metreleptin, with most patients reaching peak titer between 3 months and 9 months (77% patients).

The most frequent adverse event associated with antibodies to metreleptin is inflammatory injection site reactions. *In vitro* high-potency neutralizing activity to

metreleptin has been identified in one patient with lipodystrophy (LD) and three obese subjects without LD in the Amylin pramlintide-metreleptin program for obesity.

Overall, the BLA is acceptable from a clinical pharmacology perspective.

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

There were numerous discussions with the Agency regarding the data needed to support an application for the lipodystrophy indication. The highlights of the regulatory history for metreleptin are shown below:

- Orphan designation granted August 22, 2001
- Fast-track designation granted October 22, 2001 (unmet medical need based on NEJM publication: Efficacy and safety of leptin replacement in treatment of lipodystrophy)
- March 2006: Amylin assumed sponsorship of metreleptin from Amgen
- October 2007: Type C meeting to confirm Amylin's interpretation of Amgen's 2001 EOP2 meeting
  - Clinical package of 29 patients from NIH trials was found to be sufficient
  - Non-clinical package was found to be sufficient
  - HIV-related lipodystrophy decided to be not within the scope of the proposed indication
- May 2008: Treatment IND 101824 opened as means to expand access to metreleptin for patients with metabolic disorders associated with lipodystrophy until submission of NDA
- April 2010: Meeting with Amylin to discuss status of and projected timeline for the lipodystrophy NDA
- July 2010: The Agency indicated acceptance of Amylin's proposal to submit the application as a rolling submission
- December 2010: Clinical, non-clinical modules, draft package insert submitted
- April 2012: Chemistry (CMC) module submitted
- May-July 2012: Agency requested updated safety and efficacy data from the NIH and FHA101 studies based on more recent data cuts in order to consider the BLA submission complete.
- December 2012: The sufficiency of these data was confirmed at a pre-BLA meeting.
- March 27, 2013: Clinical data with updated data cuts submitted, along with immunogenicity assessment
- A major amendment was received on June 24, 2013 and the PDUFA clock was extended by three months with the new due date of 2/24/14.

2.1.2 *What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

Metreleptin, a recombinant analog of human leptin, is a 147-amino acid polypeptide that differs from the human leptin sequence by 1 additional amino acid, methionine, located at the amino-terminal end.

Metreleptin drug product is a sterile, white, solid lyophilized cake containing 11.3 mg of metreleptin. Prior to patient use, a vial is reconstituted with 2.2 mL of Water for Injection, USP (WFI), or Bacteriostatic Water for Injection containing 0.9% benzyl alcohol, USP (BWFI) for a final formulation of 5 mg/mL metreleptin, (b) (4) glutamic acid, (b) (4) glycine, (b) (4) sucrose, (b) (4) polysorbate 20, pH 4.25. The resulting solution is administered by subcutaneous injection. Metreleptin reconstituted in BWFI is proposed to be used for multiple doses within 3 days. Metreleptin reconstituted with WFI may only be used for a single dose.

The drug product is packaged in a 5 mL USP Type I glass vial with a (b) (4) stopper, and an aluminum seal with plastic flip-off cap. Metreleptin in vials should be stored refrigerated (2 - 8°C) and protected from light, before and after reconstitution.

Table 2: Chemistry and Physicochemical Properties of the Drug Substance

General	Metreleptin is a recombinant, non-glycosylated 16 kDa protein hormone produced recombinantly in *E.coli*. The drug substance is formulated at a final concentration of 20 mg/mL in (b) (4) glycine, (b) (4) sucrose, (b) (4) polysorbate 20 and (b) (4) glutamic acid,pH 4.25.
Chemical Formula	$C_{714}H_{1167}N_{191}O_{221}S_6$
Molecular Weight	16,156 Daltons
Amino Acid Sequence	(b) (4)
Structural Formula	Metreleptin is a 147 amino acid polypeptide with one disulfide bond between Cys-97 and Cys-147.
Solubility	pH 4 = 70 mg/mL Neutral pH = 2 mg/mL

Biological Activity	Metreleptin is biologically active in a cell-proliferation bioassay that utilizes a custom 32D OBECA (Keptin) cell line. Metreleptin binds to the receptor expressed by the cells. The cells then proliferate in a dose-dependent manner in response to the varying amounts of metreleptin. Cell proliferation is quantitated by addition of the CellTiter-Glo® reagent, which results in cell lysis and generation of a luminescent signal. The signal is proportional to the amount of ATP present, which is directly proportional to the number of viable, actively metabolizing cells prior to lysis. The potency of the sample is reported relative to the potency of the reference standard. (See chemistry review for details)

Formulation:

(b) (4) The lyophilized metreleptin drug product formulation used in Phase 2 and Phase 3 clinical studies and in primary and supporting stability studies is identical to the proposed commercial metreleptin drug product formulation (Table 3). A reconstitution diluent with a preservative (0.9% benzyl alcohol) was introduced during Phase 3 clinical studies to permit multiple dosing from the same vial.

Table 3: Overview of formulation development for metreleptin and drug product used in clinical studies

(b) (4)

Source: Sponsor's Table. Quality overall summery; Drug product overview, page 6

2.1.3 What is the mechanism of action and therapeutic indication?

Leptin is the product of the obese (ob) gene and is a naturally occurring hormone predominantly secreted by the adipocyte tissue. It plays a central role in neurohormonal regulation of energy homeostasis, fat and glucose metabolism, and other diverse physiological functions.

The lipodystrophies are a heterogeneous group of adipose tissue disorders characterized by selective loss of fat from various parts of the body. The lipodystrophies are

categorized according to both the etiology (congenital or acquired) and the pattern of fat loss, which can be either generalized (affecting the whole body) or partial (affecting specific body regions). Fat loss can be limited, resulting in well-demarcated subcutaneous depressed areas or indentations as seen in localized lipodystrophy, or extensive and widespread, with nearly complete absence of body fat, as seen in congenital generalized lipodystrophy. The extent of fat loss determines the severity of metabolic complications: patients with localized lipodystrophy have only cosmetic problems, whereas those with generalized lipodystrophy have severe insulin resistance, hypertriglyceridemia, diabetes mellitus at an early age, and fatty liver (*Garg, Excerpta Medica, 2000)*.

The loss of adipose tissue in lipodystrophy results in a state of relative leptin deficiency, analogous to other hormone deficiency conditions, which can be corrected by supplying the missing or deficient hormone. Thus, metreleptin (a recombinant human analogue of leptin) is proposed to serve as a unique therapy in patients with LD in that may partially correct the underlying pathophyisiology and improve the metabolic disorders in the LD patients.

Specifically, metreleptin is proposed to:

- Lower hepatic and myocellular lipid levels, resulting in increased insulin sensitivity.
- Improve insulin suppression of glucose production in the liver and increase insulin-stimulated peripheral glucose uptake in the muscle.
- Correct hyperphagia secondary to leptin deficiency with concomitant reduction in caloric and fat intake.

The proposed indication for this BLA is the following:

"Metreleptin is a recombinant analog of human leptin indicated for treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy."

Limitation of use: Metreleptin is not indicated for use in patients with HIV-related lipodystrophy or for use in patients with diabetes mellitus and/or hypertriglyceridemia without concurrent evidence of inherited or acquired lipodystrophy.

2.1.4 What are the proposed dosage and route of administration?

The proposed dosing recommendation is as follows:

Metreleptin should be administered by subcutaneous (SC) injection once daily.

Metreleptin should be administered into the SC tissue of the abdomen, thigh, or upper arm, and may be alternated among these sites as needed depending on amount of SC tissue in these areas.

Based on clinical response (e.g., inadequate metabolic control) or other considerations (e.g., tolerability issues, excessive weight loss [especially in pediatric patients]), the metreleptin dose may be adjusted in increments or decrements of 0.02 mg/kg for patient's ≤40 kg (Table 4). For patients >40 kg, dose may be adjusted in increments or decrements of 1.25 mg to 2.5 mg. Doses exceeding 1 mL can be administered as 2 injections (the total daily dose divided equally) to minimize potential injection site discomfort due to injection volume. When dividing doses due to volume, doses can be administered consecutively. In clinical studies, a limited number of patients received doses greater than 0.13 mg/kg for patients ≤40 kg and 10 mg per day for patients >40 kg, and therefore, there are insufficient data to recommend doses beyond these ranges.

Table 4: Metreleptin recommended daily dose by weight and gender

Baseline Weight	Daily Dose (Injection Volume)
≤ 40 kg (males and females)	0.06 mg/kg (0.012 mL/kg)
> 40 kg	
Males	2.5 mg (0.5 mL)
Females	5.0 mg (1.0 mL)

Source: Labeling; Clinical Overview page 5

2.1.5 Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?

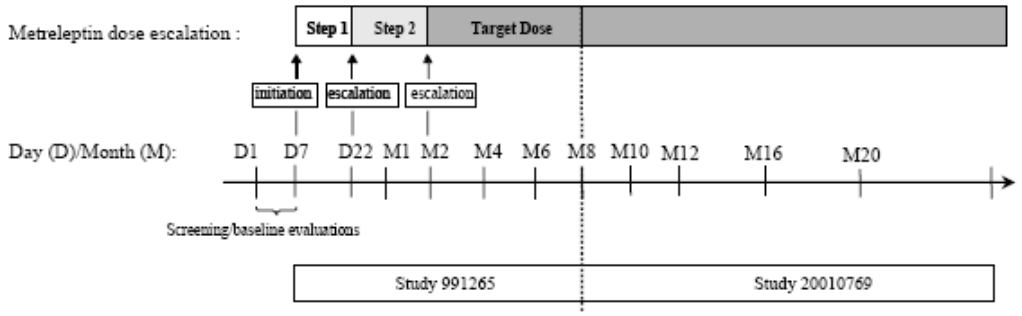
No.
The lyophilized metreleptin drug product formulation used in Phase 2 and Phase 3 clinical studies and in primary and supporting stability studies is identical to the proposed commercial metreleptin drug product formulation.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There is limited information on the PK of metreleptin in lipodystophy patients. No exposure-response has been performed. The PK disposition of metreleptin has been quantified with data from clinical trials in healthy subjects. No formal drug-drug interaction studies were conducted by the sponsor. No studies have been conducted to evaluate the PK in specific populations, e.g., renal or hepatic impairment.

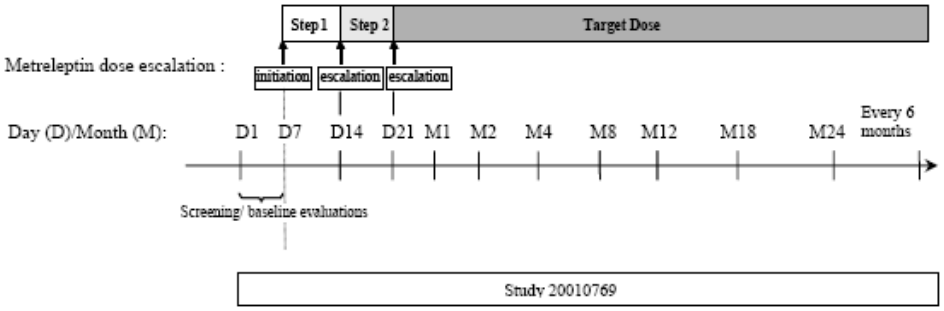
The pivotal clinical efficacy/safety trial is from the investigator initiated NIH trials 991265 (completed) and 20010769 (ongoing). The study design for the NIH trials and the supportive trial FHA101 is shown below:



[1] Metreleptin target dose was achieved via a 2-step dose escalation per protocol.
[2] Following the first metreleptin dose on Day 7, patients were observed as inpatients for at least 48 hours. Patients were not required to visit the site on Day 22
Cross-Reference: Adapted from Protocols 991265 and 20010769, 5.3.5.3, CSR, Appendix 1.

Figure 1: NIH 991269/20010769 Study Design Overview and Visit Structure for Patients Enrolled in Study 991265
Source: Clinical Efficacy Update, Page 1961.

In brief, Study 991625 was an open-label, dose escalation study to determine the safety, efficacy of short term leptin replacement (8 months) in patients greater than 14 years of age. The baseline leptin level criterion in this study was < 4 ng/mL for females and < 3 ng/mL for males.



[1] In the initial protocol metreleptin target dose was to be achieved via a 2-step dose escalation. As the study evolved over time patients who initiated later started at higher doses and required minimal dose escalation.
[2] Following the first metreleptin dose on Day 7, patients were observed as inpatients for at least 48 hours. Patients were not required to visit the site on Day 14 or Day 21
[3] Patients in Study 20010769 who continued treatment beyond 2 years were scheduled to return for follow-up visits every 6 months.
Cross-Reference: Adapted from Protocols 991265 and 20010769, 5.3.5.3, CSR, Appendix 1.

Figure 2: Study Overview and Visit Structure for Patients Enrolled in NIH Study 200107
Source: Clinical Efficacy Update, Page 1961.

In brief, Study 200107 was also open-label, long term study to determine the efficacy and safety of metreleptin in patients greater than or equal to six months of age. The

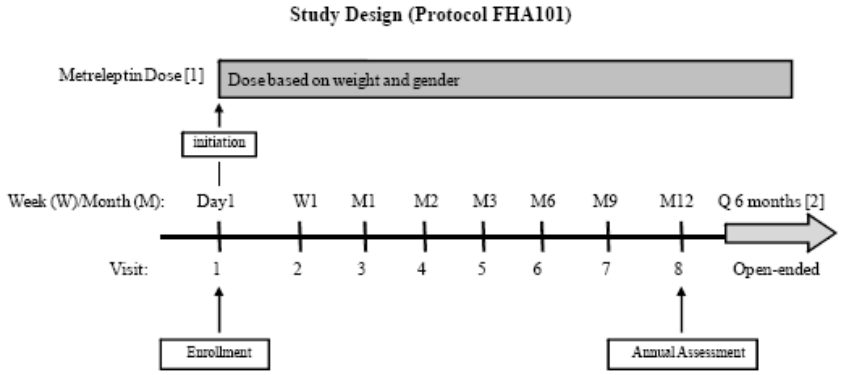
enrollment criteria for baseline leptin was higher than the previous study (<8 ng/mL for males and < 12 ng/mL for females). The key inclusion criteria are shown in Table 5.

Table 5: Key inclusion criteria

Study 991265	Study 20010769
>14 years of age, with clinically significant lipodystrophy	≥6 months of age, with clinically significant lipodystrophy [1]
Circulating leptin concentrations <4.0 ng/mL (females) or <3.0 ng/mL (males) [2]	Circulating leptin concentrations <12.0 ng/mL in females and <8.0 ng/mL in males who are ≥5 years of age. In children ages 6 months-5 years, a circulating leptin concentration of <6 ng/mL [2]
At least 1 of the following 3 metabolic abnormalities: • Presence of diabetes mellitus as defined by the 1997 ADA criteria • Fasting insulin concentration >30 μU/mL • Fasting triglyceride concentration >200 mg/dL	At least 1 of the following 3 metabolic abnormalities: • Presence of diabetes mellitus as defined by the 1997 ADA criteria • Fasting insulin concentration >30 μU/mL • Fasting triglyceride concentration >200 mg/dL or postprandially elevated triglyceride concentration >500 mg/dL when fasting is not clinically indicated (e.g., infants)

ADA = American Diabetes Association.
[1] The age limit had been >5 years from the start of the protocol until 2009, when the age limit was amended to ≥6 months.
[2] Leptin concentration was measured with a radioimmunoassay.

The design overview of the supportive trial FHA101 is shown below:



[1] Daily recommended dose: subjects ≤40 kg (0.06 mg/kg), male subjects >40 kg (2.5 mg [0.5 mL]), females >40 kg, (5.0 mg [1.0 mL]). Based on clinical response (e.g., inadequate metabolic control or excessive weight loss or tolerability issues), metreleptin dose may be adjusted in increments or decrements of 0.02 mg/kg for subjects ≤40 kg and 1.25 (0.25 mL) to 2.5 mg (0.5 mL) for subjects >40 kg.
[2] Following evaluation at the end of approximately 1 year of treatment, subjects should return to the treatment site every 6 months or as directed by the investigator until metreleptin treatment is discontinued or until the protocol is terminated for administrative or safety reasons.
Cross-Reference: Adapted from Protocols 991265 and 20010769, 5.3.5.3, Clinical Summary Report, Appendix 1.

Figure 3: FHA101 Study Design
Source: Clinical Efficacy Update, Page 1962.

Study FHA101 is an ongoing open-label study in patient's ≥ 18 years. The mean baseline leptin level in this trial was 12.9 ng/mL. 82% of the patients had partial lipodystrophy as compared to 33% in the NIH trials.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Lipodystrophy is a heterogeneous group of diseases of selective deficiency or destruction of adipocyte cells. This is associated with leptin deficiency and severe metabolic complications like insulin resistance/diabetes, hypertriglyceridemia, pancreatitis, hepatosteatosis. There is no available treatment to address the underlying basis for these metabolic complications. Typically dietary modifications, and use of anti-hyperglycemic and lipid lowering agents are used for management of glycemic and lipid control. The key endpoints selected in the NIH trials at month 12 included change in HbA1c from baseline and change in triglycerides from baseline, and fasting plasma glucose. In addition, other endpoints including fasting lipids, ALT, and AST were measured. However as there is no placebo and the natural history of the disease is not clearly defined, it is very difficult to assess the 'true' effect of metreleptin using these endpoints.

2.2.3 Are the active *moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes.

Fasting leptin levels were measured in the pivotal NIH trials. The PK of metreleptin was characterized in healthy subjects in the obesity program and has been used as supportive information in this application. PK was also characterized in the FHA101 trial. The leptin assay used does not differentiate between endogenous leptin and metreleptin and is referred as 'total' leptin. Refer analytical section for details.

2.3 Exposure-Response

2.3.1 Is there dose-response for effectiveness for metreleptin?

No.

There were a total of 72 patients in the NIH trials and 28 patients in the FHA101 trial. The trials were open-label and uncontrolled (no placebo/active control). The effects of metreleptin treatment on hemoglobin A1C (HbA1c), fasting plasma glucose (FPG), and triglycerides (TG) in patients with LD were among the primary outcome measures of NIH Studies 991265/20010769.

There are several limitations to the interpretation of the efficacy results in the pivotal trial due to the lack of placebo as well as significant confounding factors such as:

- The patients diet was not recoded and it is unknown if patients made dietary changes after enrolling in the trial. This aspect is important as changes in diet have shown to affect the endpoints that were measured in this trial, namely blood glucose and triglycerides.
- Patients were on background medications at the time of enrollment (including anti-diabetic and lipid lowering agents). The background medication changes were made in the first year as well as compliance was not recorded consistently.
- Several changes made to protocol over time with respect to enrollment criteria.
- Dosing changes were made over time (weight based dosing to fixed weight dosing; BID to QD)

Rationale for the sponsor's proposed dosing:

- Per NIH protocol, females received higher dose than males. This is also supported by the gender dimorphism of leptin levels in healthy subjects, with women having higher leptin levels than men even after adjustment for differences in body composition (*Saad, 1997: J Clin Endcrinol Metab. 82(2): 579-584)*.
- Recommended magnitude of dose adjustment is based on experience from dose titration in the NIH study. For consistency, the same increments are proposed for decreasing the dose for tolerability issues or excessive weight loss.
- Pediatrics: Sponsor has stated that the small number of younger patients studied in the NIH pivotal studies makes it difficult to generalize to all potential pediatric patients (particularly pre-adolescent children). Thus, consistent with common clinical practice for pediatric patients, a weight-based (mg/kg of body weight) dosing regimen (0.06 mg/kg) is proposed for patients weighing ≤40 kg. The proposed dose of 0.06 mg/kg was chosen as this was the target dose specified in the protocol for patients ≥ 5 years to 10 years of age. In the event of inadequate metabolic control or tolerability issues, a change in dose increment of 0.02 mg/kg is proposed, which is consistent with the NIH protocol. The rationale for selecting a cut-off of ≤40 kg is somewhat arbitrary (this was not prespecified in the protocol, which specified weight-based dosing for all patients. The basis for proposing a ≤40 kg cut-off was the intent to capture the majority of pediatric patients.
- Dosing of metreleptin evolved over time from a BID to a QD dosing regimen without compromising efficacy. A total of 32 patients in the NIH pivotal studies were initiated on BID dosing and then transitioned to QD dosing, 22 received metreleptin BID only; and 18 received metreleptin QD only. Based on this, a QD approach is proposed.
- There is limited experience for doses higher than 10 mg per day. Thus sponsor has proposed that the dose should not exceed 10 mg/day.
- Weight based vs. fixed dosing: The individual dose titration was based on individual clinical response. As the metreleptin dosing changed over the duration of the trial, the sponsor proposed a weighted average dose as follows:

Weighted average dose = Sum [Daily Dose * Dose Duration in Days] / Total Days

The following Table 6 shows the changes in HbA1c, FPG and TG over the initial year of metreleptin treatment for the overall population (Intent to treat) with observed data.

Table 6: Change From Baseline Month 4, 8, and 12 in HbA1c, FPG, and Fasting TG (NIH; ITT Population Observed Data for Each Efficacy Parameter)

Parameter	Statistic [1][2][3][4]	Month 4	Month 8	Month 12
HbA1c (%)	N	45	51	50
	Baseline Mean (SD)	8.3 (2.0)	8.4 (2.1)	8.2 (2.2)
	Change from Baseline			
	Mean (SE)	-1.1 (0.2)	-1.3 (0.2)	-1.4 (0.2)
	Median	-0.8	-1.1	-1.1
	Min, Max	-5.8, 1.8	-5.5, 1.3	-5.8, 0.9
	95% CI	-1.6, -0.7	-1.8, -0.9	-1.8, -0.9
FPG (mg/dL)	N	46	54	52
	Baseline Mean (SD)	192.1 (86.6)	176.3 (86.1)	169.8 (88.5)
	Change from Baseline			
	Mean (SE)	-45.5 (11.6)	-34.2 (9.9)	-41.8 (11.7)
	Median	-38	-26	-26
	Min, Max	-311, 125	-216, 165	-232, 271
	95% CI	-68.8, -22.1	-54.0, -14.3	-65.2, -18.4
Fasting TG (mg/dL)	N	45	52	51
	Baseline Mean (SD)	959.3 (1331.1)	1174.8 (2377.6)	1015.7 (1780.3)
	Change from Baseline			
	Mean (SE)	-472.1 (172.3)	-584.6 (285.1)	-672.9 (223.4)
	Median	-188	-58	-121
	Min, Max	-5682, 2811	-10377, 4345	-8866, 521
	Percent Change from Baseline			
	Mean (SE)	-38.0 (5.9)	-10.5 (9.4)	-31.9 (7.6)
	Median	-42.6	-23.4	-44.8
	Min, Max	-93.9, 94.2	-91.8, 287.7	-93.3, 194.4
	95% CI	-49.9, -26.2	-29.4, 8.4	-47.2, -16.6

[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time point may vary across parameters (e.g., HbA1c, FPG, and TG) as it is dependent on the number of patients with a value for that specific parameter. Also note that the N at a given time point depends on whether data for that time point is available and whether the study visit fell within the specified visit window.

[2] In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin and is calculated for those patients with values at the specified visits.

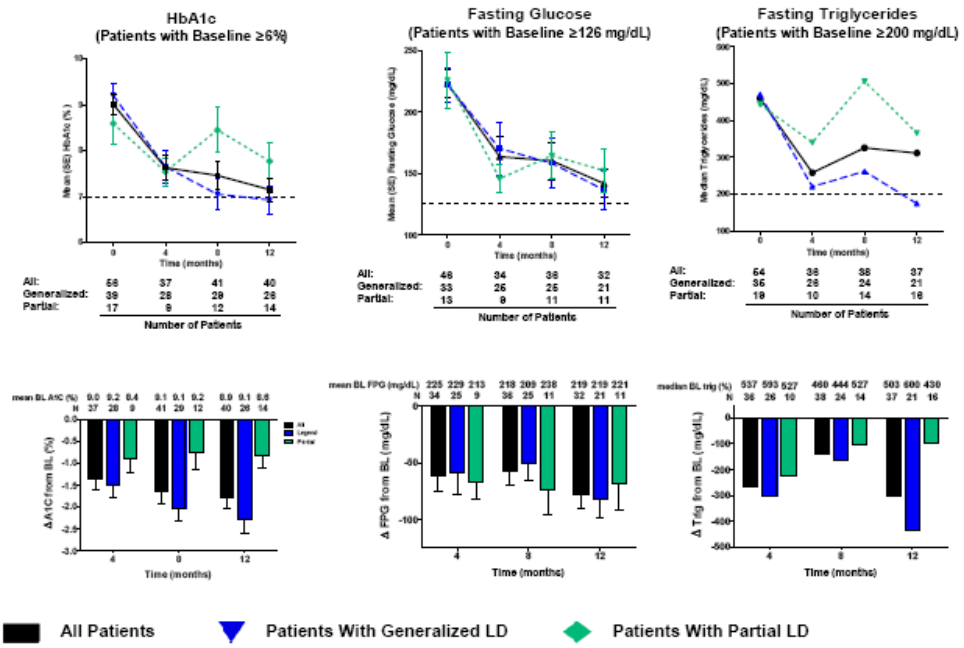
[3] 95% confidence interval from paired t-test.

[4] Mean/median change was calculated from the changes for all ITT patients with values at baseline and at the given visits.

Cross-References: NIH SDS 2.16.3, 2.16.2.2.

Source: Clinical Efficacy Update, Page 32.

Sponsor further characterized the effect of metreleptin on these parameters in patients who had elevated values of the parameter at baseline, i.e., HbA1c (≥6%), FPG (≥126 mg/dL), and/or fasting TG (≥200 mg/dL).This is further differentiated by generalized and partial LD (Figure 4).



[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time point may vary across parameters (e.g., HbA1c, FPG, and TG) as it is dependent on the number of patients with a value for that specific parameter. Also note that the N at a given time point depends on whether data for that time point is available and whether the study visit fell within the specified visit window.

[2] Dashed lines denote common treatment goals and/or diagnostic criteria for HbA1c of 7%, for FPG of 126 mg/dL, and for TG of 200 mg/dL.

Cross-References: NIH SDS 2.1.4.1, 2.2.4.1, 2.3.4.1.

Figure 4: Key Efficacy Parameters in Patients With Baseline HbA1c ≥6%, FPG ≥126 mg/dL, or TG ≥200 mg/dL: All Patients, Generalized LD, and Partial LD (NIH; ITT Population Observed Data for Each Efficacy Parameter)

Source: Clinical Efficacy Update, Page 37.

While, reductions were seen in HbA1c, FPG and TG in patients with both generalized and partial lipodystrophy, the results should be interpreted with caution due to the limitations highlighted above.

Efficacy in pediatrics:

There were 39 pediatric patients in the NIH trials and predominantly were female (77%). The mean age of the pediatric population at baseline was 12 years (range 1 yr to 17 yrs), with 17 (44%) patients ≤12 years and 22 (56%) patients between 12 > to <18 years. Baseline mean body weight and BMI for the pediatric population were 49 kg and 20 kg/m2, respectively. There was substantial overlap in the range of body weight between pediatric and adult patients (maximum for pediatric of 89 kg and minimum for adult of 39 kg).

The Table 7 shows the changes from baseline in HbA1c, FPG and TG over the initial 12 months of metreleptin treatment for the ITT pediatric patients (< 18 years). There appears to be reductions in HbA1c, FGG and TG with metreleptin treatment. Again, these reductions should be interpreted with caution due to the limitations mentioned previously.

Table 7: Change From Baseline to Month 4, 8, and 12 in HbA1c, FPG, and TG: Pediatric (<18 yrs) Patients With LD (NIH; ITT Population Observed Data for Each Efficacy Parameter)

Parameter	Statistic [1][2][3]	Month 4	Month 8	Month 12
HbA1c (%)	**N**	23	28	25
	Baseline Mean (SD)	8.4 (2.3)	8.1 (2.4)	8.1 (2.4)
	Change from Baseline			
	Mean (SE)	-1.1 (0.3)	-1.6 (0.3)	-1.6 (0.3)
	Median	-0.8	-1.1	-1.6
	Min, Max	-3.7, 1.8	-5.5, 1.3	-4.5, 0.7
FPG (mg/dL)	**N**	24	30	27
	Baseline Mean (SD)	191.6 (101.1)	156.0 (87.4)	156.7 (91.5)
	Change from Baseline			
	Mean (SE)	-38.4 (18.2)	-21.0 (12.2)	-31.0 (17.9)
	Median	-30	-13	-15
	Min, Max	-311, 125	-134, 165	-225, 271
Fasting TG (mg/dL)	**N**	24	29	27
	Baseline Mean (SD)	1042.1 (1656.4)	845.0 (1553.6)	872.3 (1594.7)
	Change from Baseline			
	Mean (SE)	-451.7 (288.1)	-463.8 (267.0)	-555.9 (259.4)
	Median	-122	-37	-115
	Min, Max	-5682, 2811	-6814, 711	-5977, 521
	Percent Change from Baseline			
	Mean (SE)	-35.0 (8.2)	-10.9 (10.1)	-23.0 (12.7)
	Median	-41.9	-13.6	-42.1
	Min, Max	-92, 94	-92, 94	-92, 194

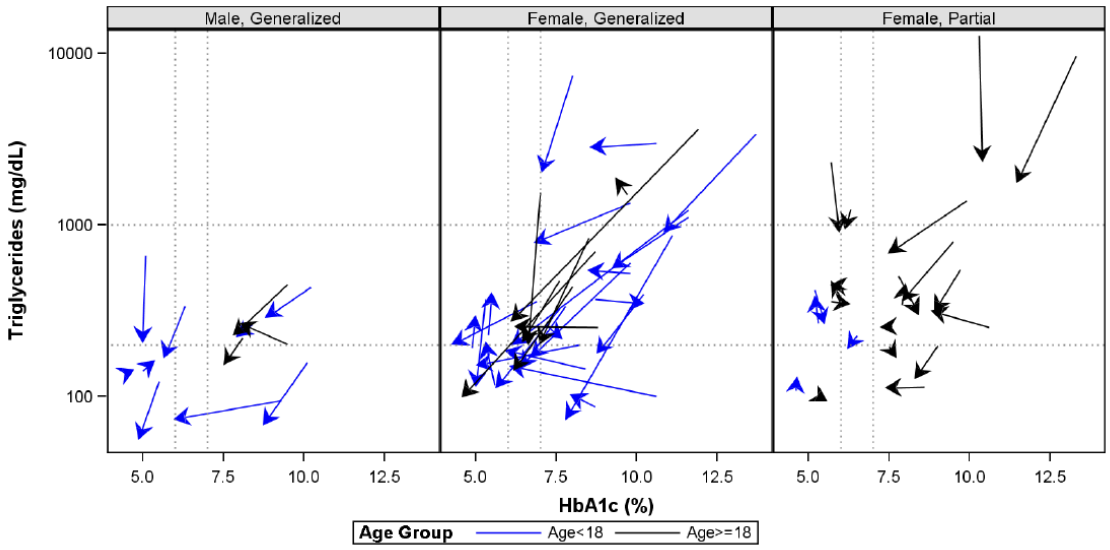
[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time point may vary across parameters (e.g., HbA1c, FPG, and TG) as it is dependent on the number of patients with a value for that specific parameter. Also note that the N at a given time point depends on whether data for that time point is available and whether the study visit fell within the specified visit window.

[2] In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin and is calculated for those patients with values at the specified visits.

[3] Mean/median change was calculated from the changes for all ITT patients with values at baseline and at the given visits.

Source: Clinical Efficacy Update, Page 58.

The Figure 5 below shows the comparison of pediatric and adult population and their magnitude of change for each of the endpoint. Overall, the changes seen are irrespective of the age and effect seems to be more for patients with higher HbA1c/TG baseline.

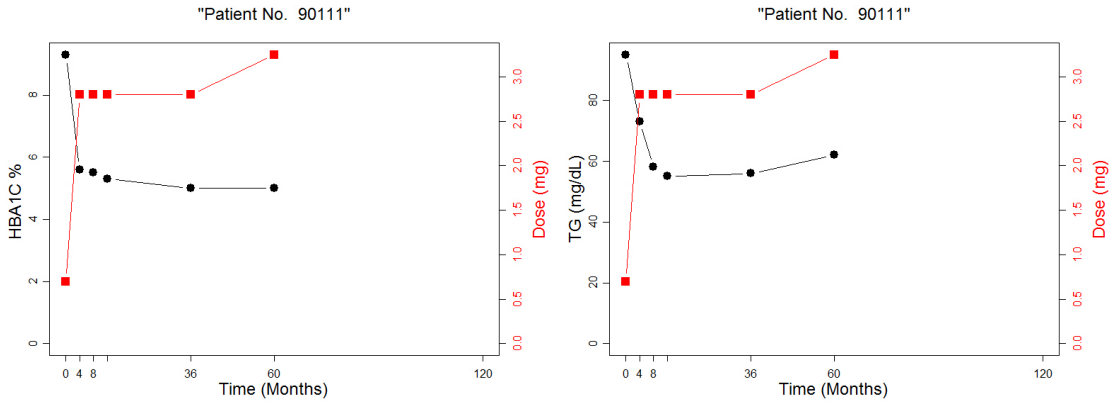


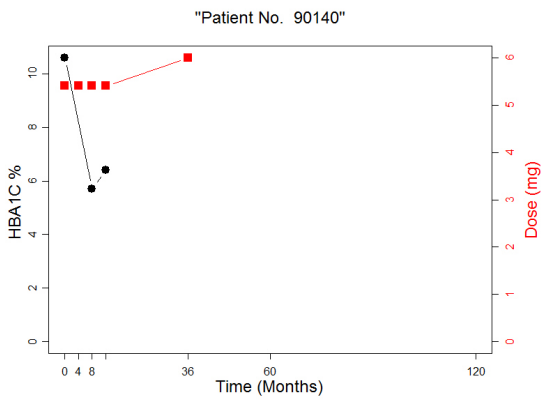
1] Horizontal Axes: HbA1c values. Vertical Axes: Triglyceride values. Arrows begin at the BL value (A1c or TG) and end with post baseline value (pointed end of arrow.)
Length of Arrow: Magnitude of change from baseline with upward arrow (increase from baseline) and downward arrow (decrease from baseline).
Dotted Lines Represent Thresholds: HbA1c: 6% (elevated) and 7% (treatment of diabetes). TG: 200 mg/dL (elevated) and 1000 mg/dL (severely elevated).

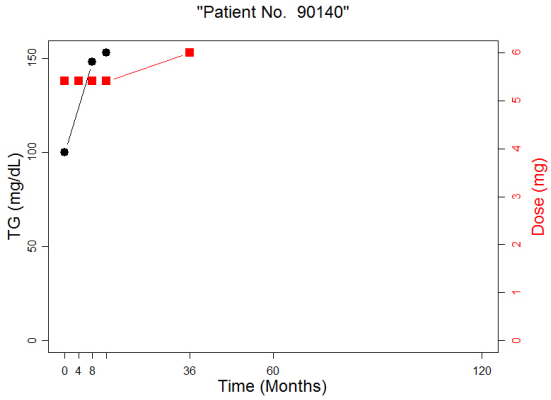
Figure 5: Change From Baseline to Mean of Postbaseline Values of HbA1c and Geometric Mean of Postbaseline Values of TG Up to 12 Months for Individual Patients by Generalized vs Partial LD, Gender, and Age (NIH; ITT Patients with Baseline and at Least 1 Postbaseline Measurement)
Source: Clinical Efficacy Update, Page 63.

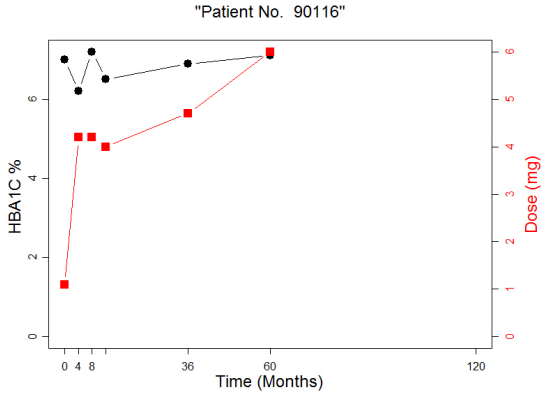
Refer to clinical review for the clinical relevance of the changes in these endpoints and other details of metreleptin efficacy.

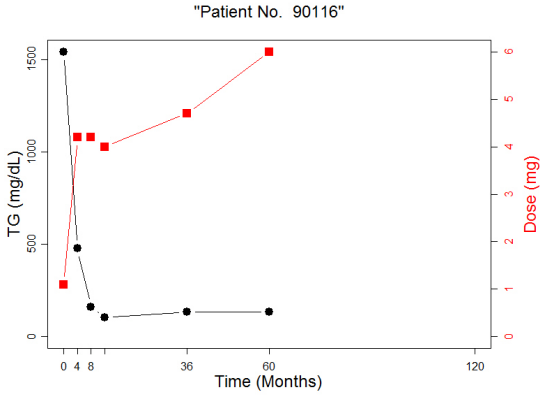
The reviewer further tried to determine if there was any dose-response to metreleptin during the first year of treatment. Based on the individual patient profiles obtained, there does not appear to be any apparent dose-response relationship for either HbA1c or TG change over time. Patients were also switched from BID to QD dosing regimen however it is unclear as to when this switch occurred with respect to visit time. Some representative patient plots are shown below (Figure 6).

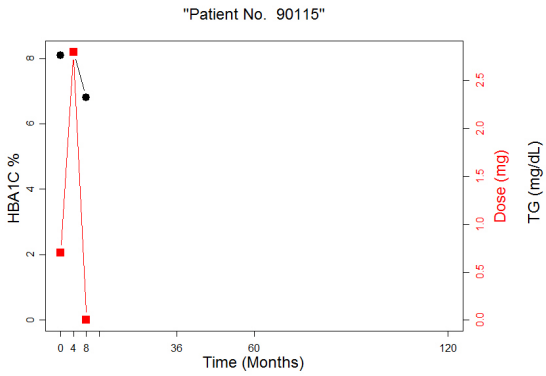


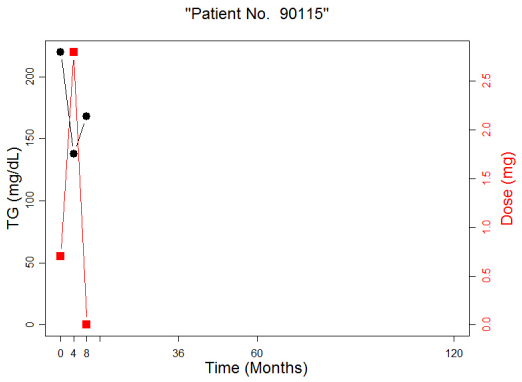

"Patient No. 90140"
HBA1C %
Dose (mg)
Time (Months)

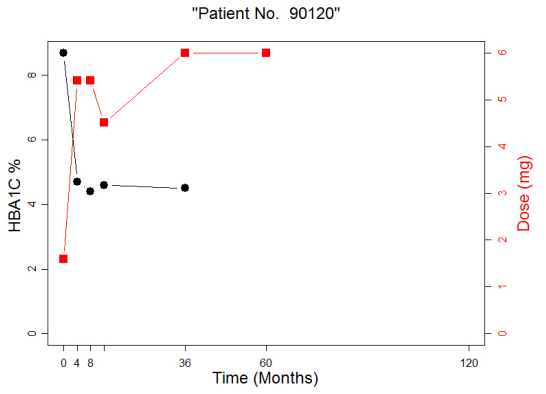

"Patient No. 90140"
TG (mg/dL)
Dose (mg)
Time (Months)

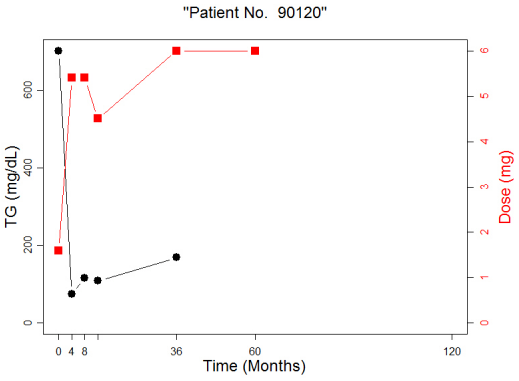

"Patient No. 90116"
HBA1C %
Dose (mg)
Time (Months)


"Patient No. 90116"
TG (mg/dL)
Dose (mg)
Time (Months)


"Patient No. 90115"
HBA1C %
Dose (mg)
Time (Months)


"Patient No. 90115"
TG (mg/dL)
Dose (mg)
Time (Months)


"Patient No. 90120"
HBA1C %
Dose (mg)
Time (Months)


"Patient No. 90120"
TG (mg/dL)
Dose (mg)
Time (Months)

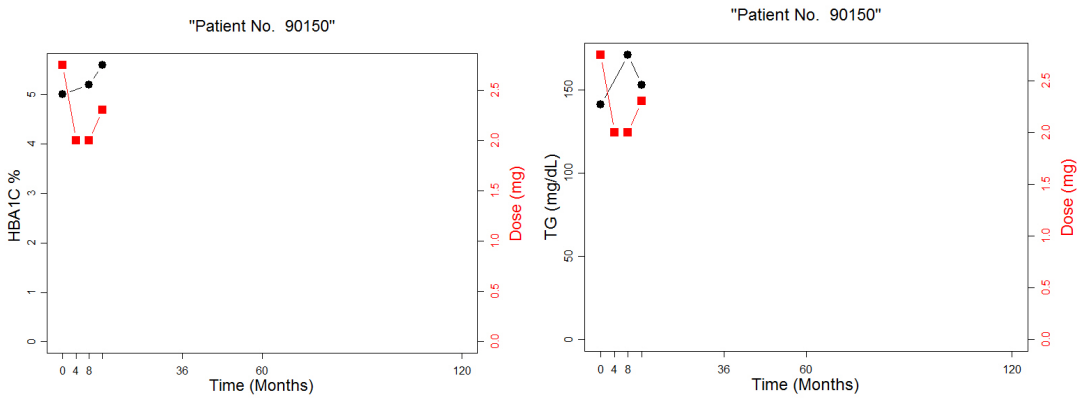
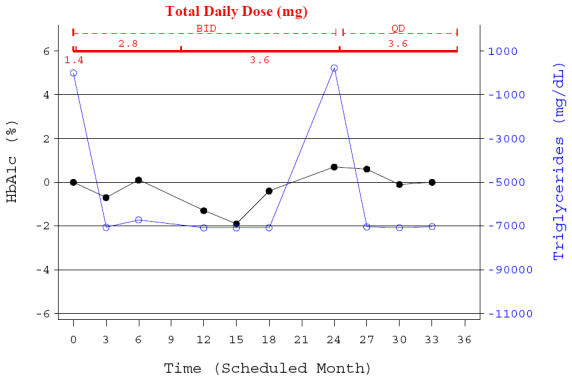


Figure 6: Individual patient change in HbA1c and TG versus duration of treatment in months

Red line indicates the dose while the black line indicated change in HbA1c (left panels) or TG (right panels)

Sponsor generated exploratory plots from study FHA101 to assess the effects of switching from BID to QD dosing on the change in HbA1c and trigycerides. Some representative individual patient plots are shown in Figure 7. As shown in the Figure 7, there appears to be no effect on the HbA1c and triglyceride response when patients were switched from BID to QD dosing.

Subject 648001



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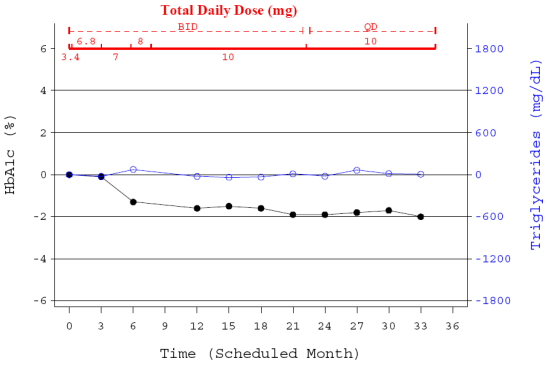

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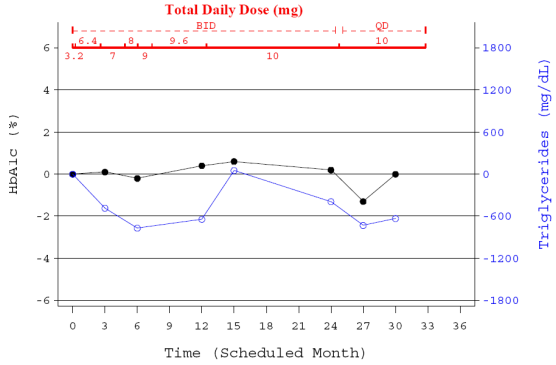
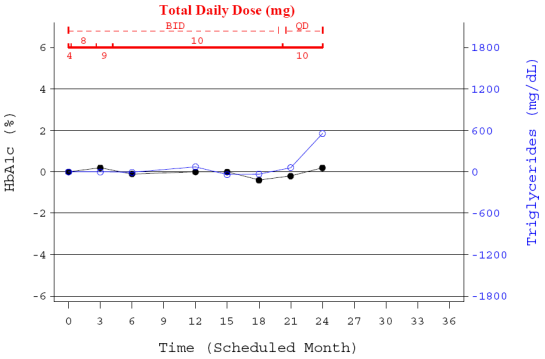
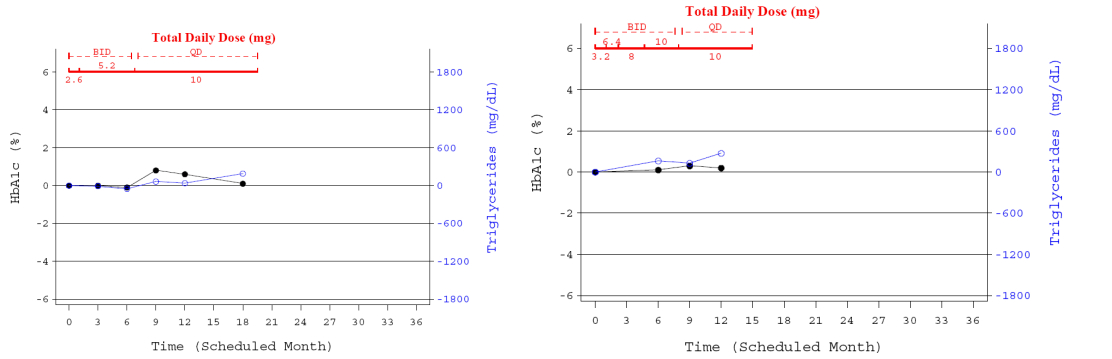


Subject 648004



Subject 648012 Subject 648013



Subject 648014 Subject 648015

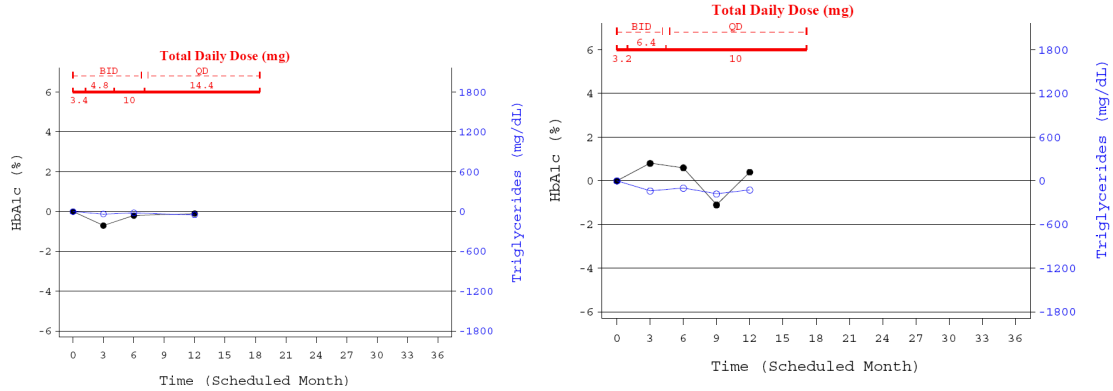


Figure 7: Individual change in HbA1c and triglycerides profiles with dosing regimen and total daily dose for study FHA101

Red line indicates the dose while the black line indicated change in HbA1c and blud line represent the change in TG values

2.3.2 What are the safety issues with metreleptin?

Leptin and cancer:

Leptin as an adipokine in preliminary work has been associated with lymphoma risk. Cytokines including leptin use the Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway for signal transduction. JAK/STATs play a critical role in immune function and hematopoiesis (*O'Shea et.al., N Engl J Med. 2013;368:161-70.*). This pathway has a central role in the signal transduction of cytokines by regulating cell proliferation, survival, and differentiation and therefore has an important role in oncogenesis (*Vasinchenker W. Oncogene 2013;32:2601–2613*). Dysregulation of this pathway contribute to the pathogenesis of some malignancies.

There is therefore, a biological plausibility for the development of lymphoma with metreleptin treatment. Two cases of peripheral T-cell lymphoma in two patients with

acquired generalized lipodystrophy (AGL) and one case of anaplastic large cell lymphoma (a type of T-cell lymphoma) also in a patient with AGL were reported in the NIH study. Also see attached the memo from the OCP safety team regarding the plausible mechanism of cancer due to leptin therapy. See clinical review for details on this risk of lymphoma and other types of cancer with metreleptin.

Immunogenicity:

Development of antibodies against exogenously administered therapeutic proteins and other biologics is well known to occur. All patients receiving metreleptin and who had antibody status assessed developed binding antibodies to metreleptin. Of the 22 patients in FHA101 study who were negative for binding antibodies to metreleptin at baseline, 21 patients developed detectable binding antibodies following exposure to metreleptin. The time to peak titer ranged from 3 months to 18 months following initiation of metreleptin, with most patients reaching peak titer between 3 months and 9 months (17 [77%] of 22 patients. The peak titer assessments have caveats as the sampling time interval of approximately 3 months may not be sufficiently frequent to capture the true peak titer.

Similarly, in the NIH trials, of the 43 patients with antibody data, 37 (86%) developed detectable antibodies following exposure to metreleptin, with peak titers ranging from 5 to 78125. The time to peak observed titer varied across patients and ranged from 1 month (Patient 90105) to 42 months (Patient 90144) following initiation of metreleptin for the time points at which samples were analyzed. As in the FHA101 trial, there was sparseness of antibody assessments that limits the interpretation.

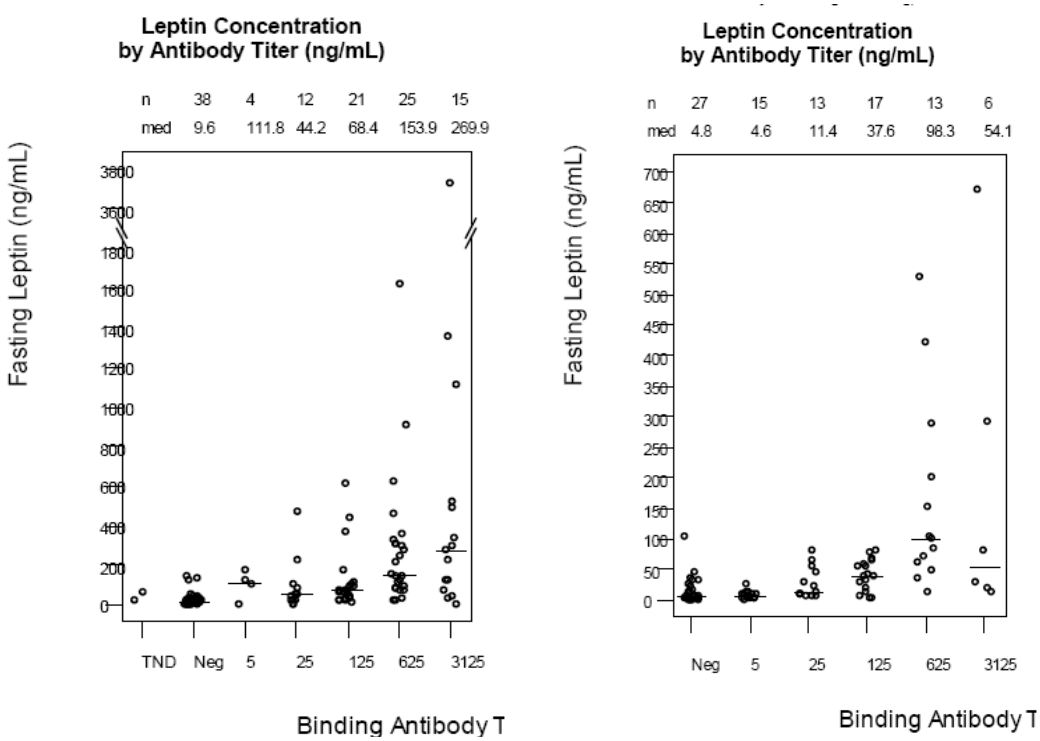
The most frequent adverse event associated with antibodies to metreleptin is inflammatory injection site reactions. In vitro high-potency neutralizing activity to metreleptin has been identified in one patient with LD and in three obese subjects without LD in the Amylin pramlintide-metreleptin program for obesity. Refer to clinical review for details on the impact of antibodies to metreleptin on its efficacy and safety.

2.3.2 What is the impact of antibodies to metreleptin on the pharmacokinetics of metreleptin?

Antibodies to metreleptin resulted in increased plasma leptin concentrations during treatment in LD patients as well as obese patients without LD. This increase in leptin concentrations may be due to delayed clearance of the metreleptin bound to the antibody, however this is confounded by the leptin assay interference by the antibodies. From the ELISA assay it was determined that samples with binding antibody titers greater than 3125 interfere with the accuracy of leptin/metreleptin quantification, i.e., plasma leptin/metreleptin concentrations associated with such titers may be lower than observed concentrations.

Figure 8 depicts fasting plasma total leptin concentration (which includes endogenous leptin and metreleptin) collected at various time points on metreleptin treatment vs.

antibody titer for the 22 patients in FHA101 with antibody data (left panel) and for the 43 patients with antibody data in the NIH trials (right panel). There appears to be an association between higher leptin concentrations and higher antibody titers although there was considerable individual variability in both the trials, especially at higher titers (Figure 8).



n = number of blood samples; med = median; TND = titer not determined (but sample confirmed positive for binding antibodies); neg = negative for binding antibodies to metreleptin.
Notes: The collection date for both leptin and antibody titer had to fall within 14 days of each other to be included in the plots.
- Fasting total leptin concentration includes endogenous leptin and metreleptin.
- One leptin value with associated titer >3125 (404 ng/ml associated with a titer of 15625 for Patient 648013) is excluded from the analysis.
- Antibody data generated using Amylin assay method

Figure 8: Fasting Plasma Total Leptin Concentrations Versus Titer of Antibodies to Metreleptin (Study FHA101, Intent-to-Treat Patients With Antibody Data [N = 22] and (NIH Studies 991265/20010769, Intent-to-Treat Patients With Antibody Data [N = 43]))
Source: Clinical Addendum, page 50 and 93.

In the PK subset of FHA101, 8-10 hour PK profiles were obtained from patients (N=13) and was stratified by the antibody titer. An increase in metreleptin concentrations (dose-normalized) was observed with increase in antibody titers of 625 and 3125 (Figure 9).

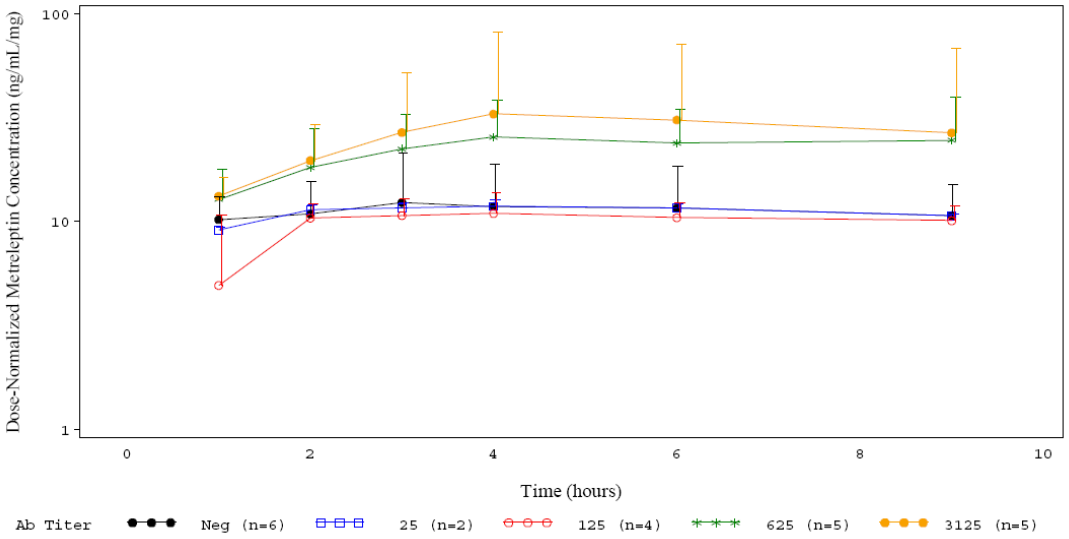


Figure 9: Mean concentration-time profiles of metreleptin stratified by antibody titer level.
Source: Sponsor study report REST120204, page 23

2.4 What are the PK characteristics of the drug?

Details on the PK of metreleptin are discussed below:

2.4.1 What are the single and multiple dose PK parameters of metreleptin in healthy adults?

Single dose PK of metreleptin:

In a 24-week study (study 950272) in healthy adult subjects with different body mass index, metreleptin was administered in 6 dose groups (0.01, 0.03, 0.1, and 0.3 mg/kg daily) as a subcutaneous injection. Plasma PK samples were collected at pre-dose, 0.167, 0.5, 1, 2, 3, 4, 5, 8, 10, 12, 18 and 24 hours after the first dose of metreleptin for the analysis of metreleptin concentrations. In general serum leptin concentrations increased with increase in dose (Figure 10). The half-life values appear to be similar across different doses. The mean PK parameters of leptin on study day 1 are shown in the Table 8 below:

Table 8. Mean (±SD) Pharmacokinetic Parameters of metreleptin on Study Day 1 in Subjects who Received metreleptin via Subcutaneous Bolus Injection

PK Parameters	Dose Group (mg/kg)					
	0.01	0.03	0.1	0.3 (5 mg/mL)	0.3 (20 mg/mL)	placebo
N	16	16	31	26	7	73
T_{max} (hr)	4.8 ± 3.9	3.8 ± 1.2	4.3 ± 1.5	4.0 ± 1.5	5.4 ± 2.4	15.0 ± 5.7
C_{max} (ng/mL)	14 ± 10	37 ± 17	119 ± 32	343 ± 104	207 ± 42	21 ± 22
$t_{1/2}$ (hrs)	4.7 ± 3.0	4.7 ± 2.0	4.3 ± 2.7	3.8 ± 1.4	3.1 ± 0.7	NA
AUC_{0-24} (ng•h/mL)	115 ± 83	321 ± 2	1120 ± 235	3511 ± 642	2036 ± 479	394 ± 421
$AUC_{0-\infty}$ (ng•h/mL)	131 ± 104	337 ± 2	1180 ± 267	3657 ± 781	2059 ± 504	850 ± 1166
$AUC_{0-\infty}$/D (ng•h/mL/mg/kg)	13099 ± 10446	11218 ± 2	11800 ± 2675	12190 ± 2603	6865 ± 1679	NA
V_z/F (mL/kg)	804 ± 634	715 ± 2	519 ± 276	444 ± 117	674 ± 150	NA
CL/F [(mL/hour)/kg]	137 ± 112	106 ± 2	89 ± 20	86 ± 18	153 ± 34	NA

NA = Not applicable

Source: Sponsor completed study report 950272, page 19 of 195

There appeared to be some differences in the Cmax and AUC of metreleptin from the 5 mg/mL and the 20 mg/mL formulations dosed as 0.3 mg/kg as noted in the Table above, although half-life is not largely different.

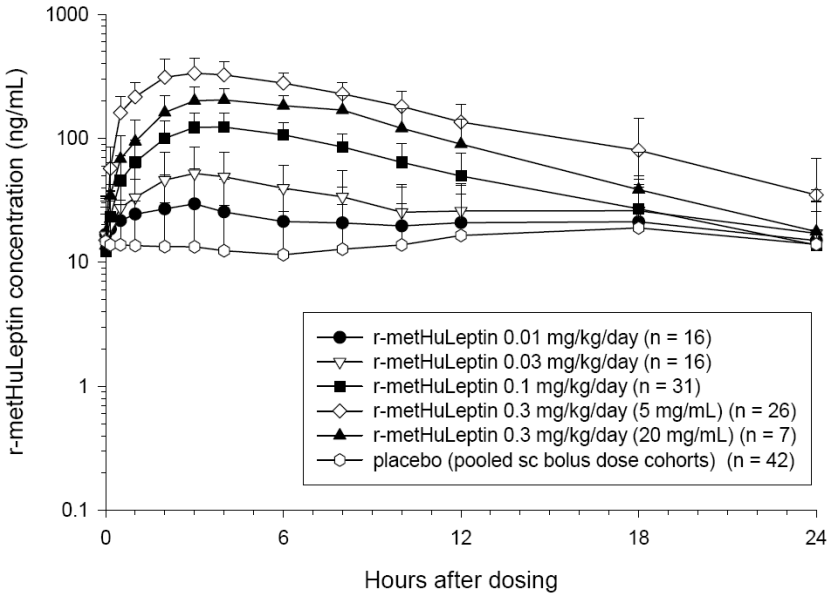


Figure 10: Mean (+SD) Total Serum Leptin Concentrations on Study Day 1 for Subjects in the SC Bolus Dose Cohorts

Source: Sponsor completed study report 950272, page 24 of 195

PK of metreleptin following multiple IV doses in subjects with a range of body mass indexes was characterized in study 970121. Subjects received once daily fixed-dose regimen (intravenous infusion) of 0.3, 1.0, or 3.0 mg/kg/day metreleptin or placebo for 28 days, or 0.1 and 0.3 mg/kg/day graduated dose for 30 days. Similar to that seen following SC administration, there appears to be increase in serum metreleptin concentrations with increasing dose following IV injection (Figure 11). The half-life was similar across the different doses and this was slightly less than that seen following SC doses. The following Table 9 shows the PK parameters after the Day1 (single dose) IV injection:

Table 9: PK parameters for the fixed and graduated dose groups after Day 1 IV injection (single dose)

	Fixed Dose (mg/kg/day)				Graduated Dose (mg/kg/day)		
	0.3	1.0	3.0	placebo	0.1	0.3	placebo
N	27	14	12	33	6	9	8
C_{avg} (ng/mL)	162.1 ± 30.8	521.1 ± 100.5	1361.2 ± 299.3	11.3 ± 11.3	56.4 ± 11.7	161.9 ± 37.4	22.7 ± 26.2
$C_{5\ min}$ (ng/mL)	4704.8 ± 928.7	13954.8 ± 2234.5	27887.4 ± 4053.3	-	1605.2 ± 331.0	4580.4 ± 910.9	-
C_{max} (ng/mL)	6160.0 ± 1385.9	17582.0 ± 2913.8	32887.3 ± 4976.2	13.9 ± 13.6	2128.5 ± 423.8	5858.8 ± 1289.0	27.1 ± 31.1
nC_{max} (ng/mL per mg/kg/day)	20533.4 ± 4619.6	17582.0 ± 2913.8	10962.4 ± 1658.7	-	21284.9 ± 4238.2	19529.4 ± 4296.5	-
$t_{1/2}$ (hrs)	3.34 ± 1.88	3.41 ± 0.85	3.42 ± 0.82	-	2.97 ± 1.58	3.78 ± 1.79	-
AUC_{0-24} (ng•h/mL)	3890.6 ± 739.2	12505.5 ± 2413.0	32669.4 ± 7183.3	272.2 ± 271.2	1354.8 ± 280.0	3884.9 ± 896.7	544.7 ± 627.7
$AUC_{0-\infty}$ (ng•h/mL)	3908.8 ± 754.1	12544.7 ± 2449.2	32775.7 ± 7250.7	-	1360.8 ± 281.6	3905.1 ± 898.7	-
CL [(mL/kg)/hr]	79.6 ± 16.1	82.5 ± 15.6	95.8 ± 21.6	-	76.6 ± 18.0	79.9 ± 15.3	-
V_z (mL/kg)	370 ± 184	398 ± 92	463 ± 116	-	331 ± 201	433 ± 240	-
V_{ss} (mL/kg)	145 ± 32	163 ± 32	204 ± 36	-	145 ± 46	153 ± 68	-
MRT (hrs)	1.9 ± 0.5	2.0 ± 0.3	2.2 ± 0.3	-	2.0 ± 0.8	2.0 ± 0.9	-

Source: Sponsor completed study report 970121, page 133 of 1592

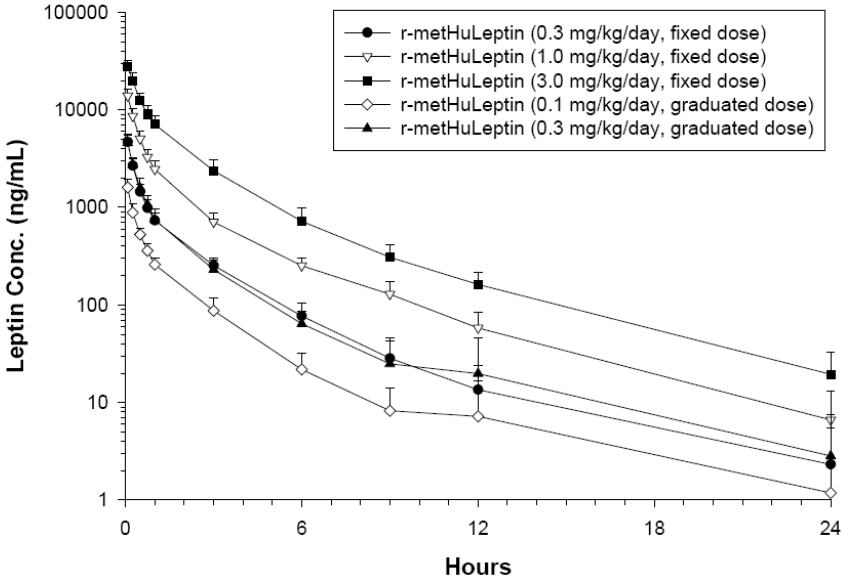


Figure 11. Day 1 Baseline Mean (+SD) Leptin Concentrations (ng/mL) of Subjects in Study LEPT-970121

Source: Sponsor completed study report 970121, page 157 of 1592

Multiple-dose PK of metreleptin:

Trough serum metreleptin concentrations on study days 1, 7, 14, 21, and 28 following SC dosing for all dosed subjects in the above mentioned study 950272 were collected and in general, serum metreleptin concentrations remained at steady state during the sampling times.

In study 970121, daily IV fixed doses of 0.3, 1.0, and 3.0 mg/kg/day were administered to subjects over a 28-day period. Similar to the single dose results, there was less than dose-proportional increase in metreleptin AUC and Cmax (Figure 12). The mean Day 15 to Day 1 metreleptin Cmax ratios were 0.9, 0.9 and 1.0 for 0.3, 1.0 and 3.0 mg/kg/day, respectively. The mean Day 15 to Day 1 metreleptin AUC ratios were 1.9, 1.0 and 1.0 for 0.3, 1.0 and 3.0 mg/kg/day, respectively. Except for the 0.3 mg/kg/day dosing group, the results suggested that there was no accumulation of r-metHuLeptin upon 15-day multiple intravenous injection dose in healthy subjects. The following Table 10 shows the mean pharmacokinetic parameters for the fixed dose group and for the corresponding placebo group after the Day 15 (Multiple Dose) injection:

Table 10: PK parameters following multiple IV injections

	Fixed Dose (mg/kg/day)			
	0.3	1.0	3.0	placebo
N	29	13	12	33
C_{avg} (ng/mL)	305.1 ± 325.5	515.0 ± 85.5	1370.7 ± 260.8	9.3 ± 10.6
$C_{5\ min}$ (ng/mL)	4566.3 ± 1371.2	13287.8 ± 2285.6	27155.8 ± 4077.5	-
C_{max} (ng/mL)	5533.0 ± 1556.7	16367.4 ± 2971.0	32055.5 ± 4883.7	11.1 ± 12.1
nC_{max}(ng/mL per mg/kg/day)	18443.4 ± 5189.0	16367.4 ± 2971.0	10685.2 ± 1627.9	-
$t_{1/2}$ (hrs)	2.18 ± 1.63	2.18 ± 0.42	2.01 ± 0.38	-
$AUC_{0\text{-}24}$ (ng•h/mL)	7322.6 ± 7811.8	12359.3 ± 2052.1	32896.2 ± 6259.7	83.9 ± 95.4
$AUC_{0\text{-}\infty}$ (ng•h/mL)	7406.6 ± 7961.6	12364.2 ± 2051.0	32906.4 ± 6260.2	-
CL [(mL/kg)/hr]	68.4 ± 32.0	82.9 ± 13.6	94.5 ± 19.2	-
V_z (mL/kg)	186 ± 178	263 ± 81	275 ± 86	-
V_{ss} (mL/kg)	147 ± 206	149 ± 36	179 ± 39	-
MRT (hrs)	2.6 ± 2.7	1.8 ± 0.2	1.9 ± 0.3	-

Source: Sponsor completed study report 970121, page 134 of 1592

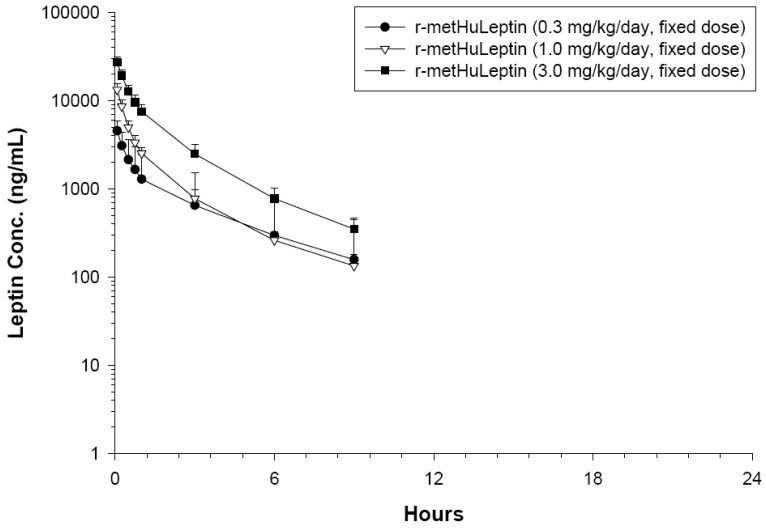


Figure 12: Day 15 baseline subtracted Mean (+SD) Leptin Concentrations (ng/mL) of Subjects in Study LEPT-970121

Source: Sponsor completed study report 970121, page 158 of 1592

2.4.2 How does the PK of metreleptin in lipodystophy patients compare to that in healthy volunteers?

There is very limited information of the PK of metreleptin in LD patients. The fasting plasma concentrations of total leptin (endogenous leptin plus metreleptin) were measured in the NIH studies. The PK properties of metreleptin in lipodystrophy patients were assessed in a subset of patients from Study FHA101. Study FHA101 was amended to include the option of collection of two pharmacokinetic (PK1 and PK2) profiles over an 8 to 10 hour time frame approximately 3 months apart, based on the discretion of the investigator. A total of 22 patients from Study FHA101 had fasting plasma leptin concentrations and/or 8 to 10 hour PK profiles for metreleptin. There were 13 patients with 8 to 10 hour PK profiles, however only five patients had an 8-10 hour PK profile after the first dose of metreleptin (i.e., metreleptin naïve). Due to the limited number of LD patients with PK measurements, the assessment of PK exposure relationships for metreleptin was primarily limited to graphical presentation.

In the clinical trials, plasma leptin levels increased during treatment with metreleptin. Figure 13 below shows the leptin levels at baseline and at month 12 for patients with available data in FHA101. It should be noted that among the patients with leptin concentration data at Month 12, the antibody titers ranged from negative to 3125. Data with antibody titers greater than 3125 were not analyzed by the sponsor due to interference with leptin assay.

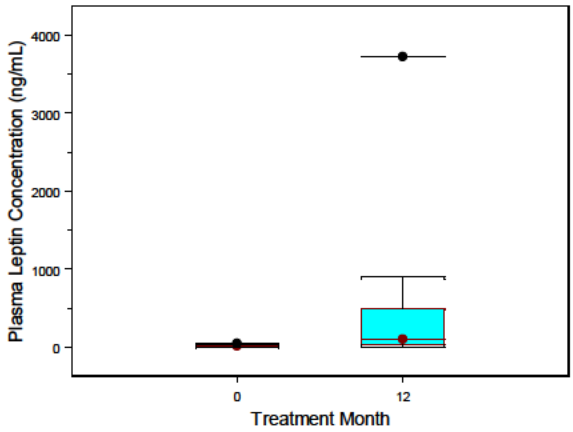
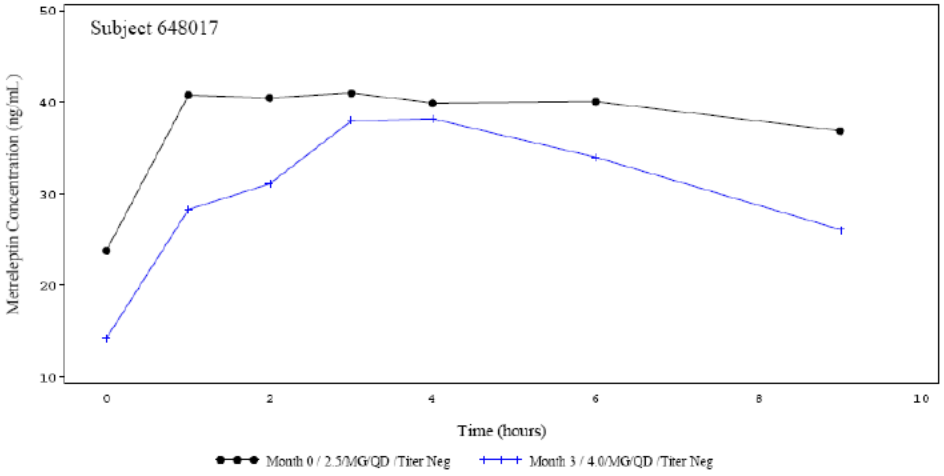
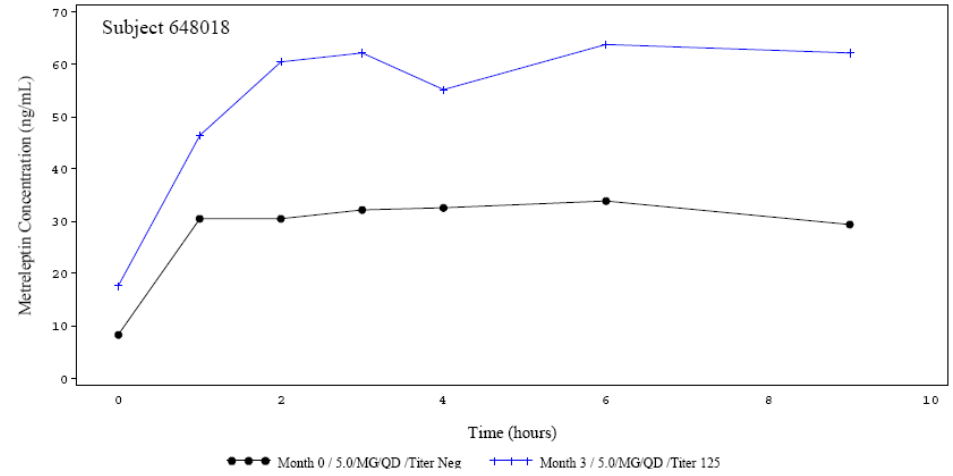
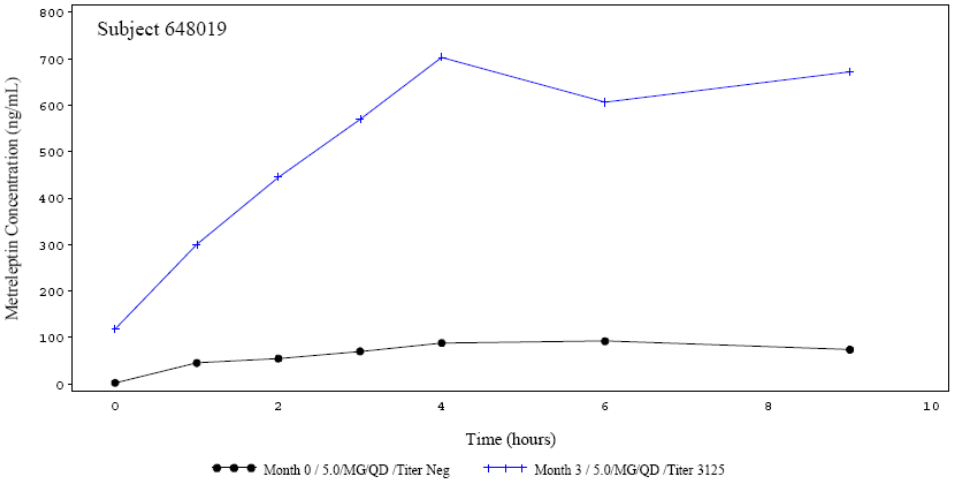


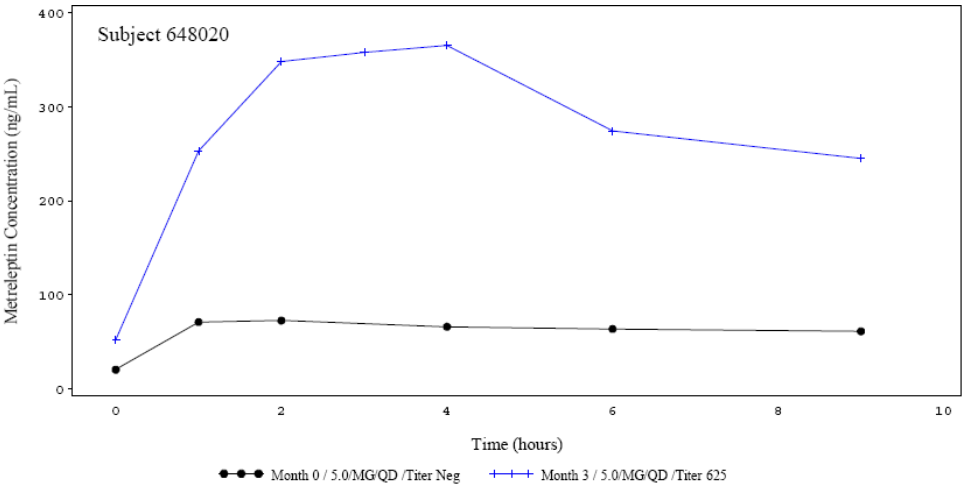
Figure 13: Plasma leptin concentration in FHA101 in LD patients at Baseline and Month 12 following metreleptin treatment

In the five patients who had PK sampling after the first dose of metreleptin and after three months, comparison of the PK profiles shows an increase in the metreleptin concentrations over time and this was also consistent with higher metreleptin antibodies (Figure 14).




Subject 648018
Metreleptin Concentration (ng/mL)
Time (hours)
Month 0 / 5.0/MG/QD /Titer Neg
Month 3 / 5.0/MG/QD /Titer 125


Subject 648019
Metreleptin Concentration (ng/mL)
Time (hours)
Month 0 / 5.0/MG/QD /Titer Neg
Month 3 / 5.0/MG/QD /Titer 3125


Subject 648020
Metreleptin Concentration (ng/mL)
Time (hours)
Month 0 / 5.0/MG/QD /Titer Neg
Month 3 / 5.0/MG/QD /Titer 625

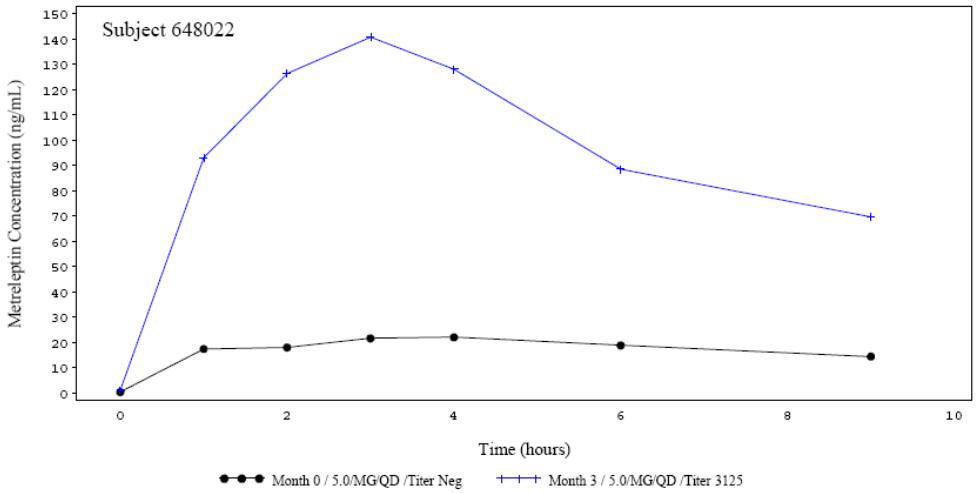


Figure 14: Individual Concentration-Time Profiles of Metreleptin for Lipodystrophy Patients from Study FHA101
Source: Sponsor study report REST120204, page 20-22

2.4.3 What are the characteristics of drug absorption?

Metreleptin is absorbed with a median Tmax of 4 hours in LD patients (FHA101, range 2-6 h). The median Tmax in the obese subjects without LD was also 4 h (range 2-8 h study 950272) following SC administration.

2.4.4 What are the characteristics of drug distribution?

The volume of distribution of metreleptin in healthy adult subjects following a single IV injection at doses of 0.3, 1.0 and 3.0 mg/kg/day was 370, 398, and 463 mL/kg, respectively. The volume of distribution on Day 15 following multiple IV injections was 186, 263 and 275 mL/kg, respectively for the 0.3, 1.0 and 3.0 mg/kg/day, doses (Study 970121, Tables 9 & 10).

2.4.5 What are the characteristics of drug elimination and metabolism?

Leptin is a protein and is cleared by renal route. Nonclinical data suggest renal clearance is the major route of metreleptin elimination, with no apparent contribution of systemic metabolism or degradation. Following multiple IV injections of metreleptin in healthy adults, terminal half-life values among the different dosing regimens (0.3-3.0 mg/kg/day) appeared to be similar. Serum leptin concentrations declined mono-exponentially, with a half-life of approximately 3.3 to 3.4 hours and a total body clearance (CL) of 80.0 to 96.0 mL/kg/h. The half-life of metreleptin following single dose in lipodystrophy patients was ~4 hours.

2.5 Intrinsic Factors

2.5.1 What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

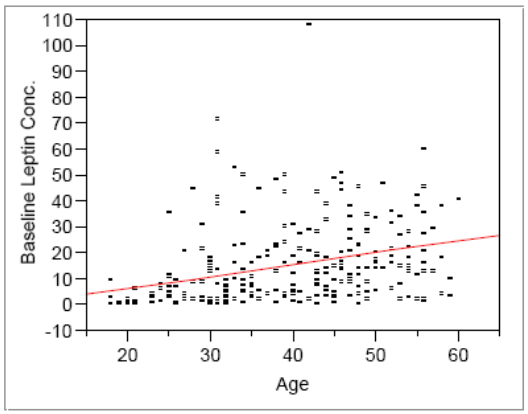
Effect of Age, Weight and Gender:

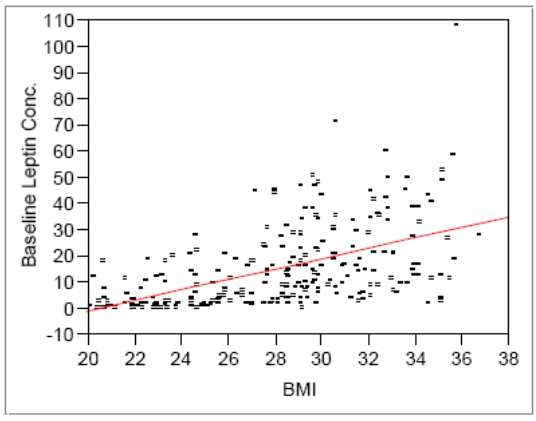
No studies were conducted to determine the effect of intrinsic factors on the PK of metreleptin in LD patients.

Saad et. al., have reported sexual differences in plasma leptin concentrations (*J Cli Endocrino Metab (82): 579-584, 1997*) The fasting plasma leptin concentration ranged from 1.8–79.6 ng/mL, with a geometric mean of 12.4 (95% CI, 11.3–13.6). Women had, on the average, 3-fold higher leptin levels than men [20.3 ng/mL (CI, 18.5–22.3) *vs.* 7.0 (CI, 6.4 –7.7); *P*, 0.001]. After adjusting for percent body fat, women continued to have approximately 40% higher leptin levels [14.4 ng/mL (CI, 13.3–15.5) *vs.* 10.3 (CI, 9.5–11.2); *P*, 0.001].

Effect of some of the covariates was analyzed in healthy subjects (study 950272). The age, weight, height and BMI of the subjects enrolled in this study ranged from 18 to 60 years, 50.2 to 122.7 kg, 1.50 to 1.94 m, and 20.1 to 36.8 kg/m2, respectively. Analysis of covariance (ANCOVA) was performed to test the effects of age, race, sex and BMI values at baseline on baseline serum leptin levels and metreleptin levels.

Sex and BMI were found to have a statistically significant effect on baseline serum leptin levels, with higher baseline serum leptin levels in females than in males, and an increase in baseline serum leptin levels with an increase in BMI. Age was not a significant factor in determining baseline serum leptin levels (Figure 15).





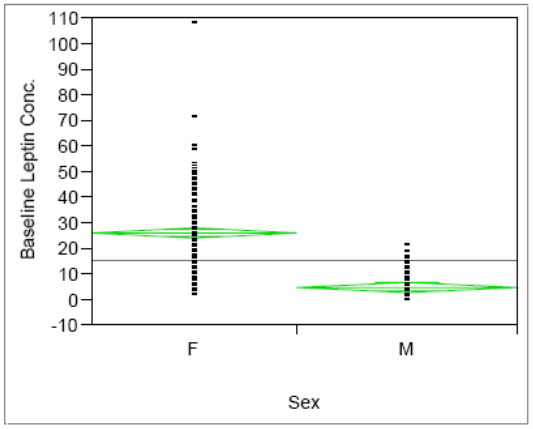


Figure 15: Effect of age, gender and BMI on baseline leptin levels in healthy subjects in study 950272
Source: Sponsor completed study report 950272, pages 182-184 of 195

In subjects who were dosed with metreleptin via SC bolus injection, sex and BMI had a statistically significant effect on dose-normalized AUC0-24h, which was found to be higher in subjects with a higher BMI and who were female. Sex was statistically significant in effecting dose-normalized Cmax with females showing higher maximum serum leptin levels than males. BMI has a statistically significant effect on CL/F value that was higher with decreasing BMI.

Hepatic Impairment:

No PK studies were conducted in hepatic impairment patients. Based on preclinical studies in animals, it is speculated that metreleptin is primarily eliminated by renal route in humans and therefore hepatic impairment is not expected to alter its PK significantly.

Renal impairment:

No PK studies were conducted in renal impairment patients. However, it is expected that the PK may be altered in LD patients with renal impairment as metreleptin is primarily hypothesized to be eliminated by the renal route based on nonclinical studies.

Javor et al., (J Clin Endocrino Metab 89(7):3199-3207) evaluated a cohort of patients with inherited and acquired generalized lipodystrophy from NIH pivotal studies 991265/20010769 over 4-36 months. They reported that the median baseline creatinine clearance (CRCL) was 205 mL/min*1.73m$_2$, with 23 out of 25 patients (92%) having an elevated CRCL (>125 mL/min*1.73m$_2$). They report that at baseline these patients also had elevated urine albumin and macroalbuminuria. The authors interpreted this elevated CRCL as renal hyperfiltration in conjunction with poorly controlled diabetes. Further, the authors conclude that in 11 of 15 patients, on leptin therapy there was a reduction in proteinuria and reduction in CRCL indicating correction of hyperfiltration.

2.5.2 What pregnancy and lactation use information is available?

No studies were conducted in pregnant or lactating women.

2.6 Extrinsic Factors

Drug-Drug Interactions:

No drug-drug interaction studies have been conducted with metreleptin.

Watson et al. (*DMD 1999, Vol 27 (6): 695-700*) investigated the alterations of several hepatic cytochrome P-450 (CYP), conjugation, and antioxidant enzymes in lean and ob/ob mice and the role leptin plays in the modulation of these enzymes. The results of this study demonstrate alterations in constitutive expression of CYP2B, CYP2E, CYP2A, catalase, glutathione peroxidase, and glutathione reductase in ob/ob mice that were restored to lean control values following leptin treatment. Additionally, CYP3A activity was increased following leptin treatment in ob/ob mice.

Literature data suggests that based on the structure of leptin and its receptor, leptin can be classified as a cytokine. Upon leptin binding to its receptor, receptor dimerisation occurs and leading to activation of signaling involving Janus kinase family and signal transducers and activators of transcription (JAK/STAT) pathways resulting in stimulation of transcription of responsive target genes. Thus leptins share some signaling pathways characteristic for the class I cytokine receptor family [*Margetic et al., In J Obesity (2002)26, 1407-1433*]. Leptin and its receptor share structural and functional similarities with members of the long-chain helical cytokines, which include interleukin (IL)-6, IL-11, IL-12, leukemia inhibitory factor (LIF), granulocyte-colony stimulating factor (G-CSF), ciliary neurotrophic factor (CNTF), and oncostatin M (OSM) (*J of Leukocyte Biology, 2000 (68); 437-446*).

The FDA DDI guidance recommends that if the investigational therapeutic protein is a cytokine or cytokine modulator, *in vivo* studies should be conducted to determine the therapeutic protein's effect on CYP enzymes and transporters. It is not known how metreleptin (considered a cytokine) will affect the concomitant drugs PK in LD patients. The LD patients are on concomitant medications (predominantly anti-diabetic and lipid lowering). Some of the concomitant medications in the NIH trials include insulin, metformin, thiazolidinediones, fibrates and statins. Considering the nature of the disease as well as the limited number of patients, it is recommended that the label should include language to reflect the potential for interaction with substrates for CYP and transporters.

Recommended language: *Leptin is a cytokine and has the potential to alter the formation of CYP450 enzymes. The effect of metreleptin on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of MYALEPT, in patients*

being treated with these types of agents, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the agent adjusted as needed. Prescribers should exercise caution when MYALEPT is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc.

2.7 General Biopharmaceutics

2.7.1 How is the proposed to-be-marketed formulation linked to the clinical trial formulation?

(b) (4) The lyophilized metreleptin drug product formulation used in Phase 2 and Phase 3 clinical studies and in primary and supporting stability studies is identical to the proposed commercial metreleptin drug product formulation (Table 3). A reconstitution diluent with a preservative (0.9% benzyl alcohol) was introduced during Phase 3 clinical studies to permit multiple dosing from the same vial.

2.8 Analytical

2.8.1 What bioanalytical methods are used to assess concentrations?

Analysis of leptin concentrations for obesity programs studies, 950272 and 970211 was conducted at Amgen. For the NIH studies 991265/20010769 in LD patients, the analyses of binding antibodies and metreleptin neutralizing activity were conducted at Amgen for the initial part of the studies (prior to Amylin assuming sponsorship), and the leptin concentration analysis was performed at the NIH (Bethesda, MD). All these analyses were conducted using samples that were not necessarily maintained under GCP conditions. For Study FHA101 in LD patients, the analyses of binding antibodies and leptin concentration were conducted at (b) (4) while the analysis of neutralizing activity was conducted at (b) (4). These assays were conducted under GLP conditions. Leptin concentrations for the LD program were measured by a radioimmunoassay (RIA) at the NIH for the NIH studies and with an enzyme-linked immunosorbent assay (ELISA) at (b) (4) for Study FHA101. Additionally, the Amgen leptin ELISA method yielded leptin concentrations in the Amgen obesity studies similar to those determined in the Amylin obesity studies; and the Amylin obesity studies measured leptin concentrations with the same ELISA kit method used at (b) (4).

It should also be recognized that all the three assays detect both endogenous leptin and metreleptin.

The NIH leptin RIA method and the [redacted] leptin ELISA method were kit assays made by the same manufacturer [redacted] [previously known as [redacted]]), which has determined that both kits measure leptin similarly. The ELISA kit insert lists a correlation with the RIA kit as having a slope = 1.456, intercept = -3.288, and correlation r = 0.985, implying results from each assay are generally comparable. Therefore, it can be inferred that the 3 leptin methods yield generally similar leptin concentrations.

NIH studies: For NIH Studies 991265/20010769, leptin concentrations were measured at NIH by an RIA that uses an [redacted] assay kit. The RIA assay recognizes both endogenous human leptin and circulating metreleptin. The assay had an LLOQ of 5 ng/mL and an ULOQ of 100 ng/mL; samples above the ULOQ were diluted to the standard curve range. The samples runs were in duplicate. The % CV for within and between assay variations was 3.4 to 8.3% and 3% to 6.2%, respectively. The recovery of leptin in human serum was ~100%. Effect of serum dilution was tested and the results were >92% of expected for all the samples tested.

FHA101: For this ELISA, it has been determined that samples with binding antibody titers greater than 3125 interfere with the accuracy of leptin/metreleptin quantification, i.e., plasma leptin/metreleptin concentrations associated with such titers may be lower than actual concentrations. In brief, the effect of antibodies to metreleptin on the quantification of total leptin in human plasma was determined using a subset of plasma samples from clinical studies in obesity program (DFA101 and DFA102). The samples was selected by antibody titer and tested undiluted, diluted 1:10 and 1:100 and spiked with metreleptin to determine a spiked recovery by which an antibody interference effect could be assessed. The results indicated that samples tested undiluted in the AC164594 IEMA method could be accurately quantified for total leptin concentrations with antibody titers of 25 or less. Samples tested undiluted with antibody titers greater than 25 revealed interference with total leptin quantification. When samples were diluted at a minimum of 1:10, total leptin could be accurately quantified in samples with antibody titers up to and including 3125.

The leptin ELISA details are shown in Table.

Assay Methodology Summary	
Analyte	Metreleptin, AC164594
Method Validation Report	TCAR09-013
Matrix	Human Plasma
Anticoagulant	K_2EDTA
Method of Detection	ELISA
Regression, Weighting	Five Parameter Curve Fit (5PL) weighted $1/Y^2$
Analytical Systems Software	SoftMax® Pro GxP v5.0.1 (Molecular Devices), Watson Bioanalytical LIMS™ v7.3.0.01 (Thermo Fisher Scientific)
Statistics Systems Software	Microsoft® Office Excel® 2007
Calibration Range	0.25* (0.3), 0.7, 1.0, 2.0, 5.0, 10.0, 20.0, 50.0, 70.0, 100.0 ng/mL
LLOQ	0.7 ng/mL
ULOQ	70.0 ng/mL
Dilution Factors Employed	10 and 100
Calibration Standard	One set of calibration standards were included on each run.
Quality Controls	One set of each level of Buffer QCs; two sets of each level of Plasma QCs; three sets of PUHQC at 1:10 and one set of PUHQC at 1:100 (if required).
Results Reporting	Statistical results were reported in a manner consistent with Watson Bioanalytical LIMS™ v7.3.0.01 and Microsoft® Office Excel® 2007. Data capture of optical density reported in SoftMax® Pro GxP v5.0.1.

Source: Report REST120087

Obesity studies: Samples in Clinical Study LEPT-950272 and 970121 were determined using a conventional solid phase sandwich EIA assay that was performed in the former at Amgen Inc. (Thousand Oaks, California). This assay does not distinguish between endogenous leptin and r-metHuLeptin, and therefore the results are a measure of both endogenous leptin and r-metHuLeptin serum levels, referred to throughout this report as "total serum leptin". The assay specifications were as follows:
Linearity is in the range of 0.04 ng/mL in study 950272 and 0.02 ng/mL in study 970121) to 10 ng/mL. The Intra-assay coefficient of variation was from 1.1 to 9.6% with a mean of 2.8%. Inter –assay CV% was from 7.8 -15.2% with a mean of 11.8%, Leptin in serum samples was stable over a variety of storage conditions over a period of seven weeks and five freeze/thaw cycles. The mean recovery was 92%.

3 Detailed labeling recommendation

The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included.

7 DRUG INTERACTIONS

No formal drug interactions studies were performed. No *in vitro* metabolism studies were performed.

3 Pages Of Draft Labeling Have Been Withheld In Full As b4(CCI/TS) Immediately Following This Page

4 Appendix

4.1 Memo from OCP safety team

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY
PREDICTIVE SAFETY TEAM

DATE: July 3, 2013
FROM: Keith Burkhart, MD
SUBJECT: Metreleptin BLA Safety Review
TO: Jayabharathi Vaidyanathan
THROUGH: Darrell Abernethy, MD, PhD, Associate Director for Safety

Thanks for contacting the Predictive Safety Team (PST) about metreleptin, an analog of human leptin. Amylin Pharmaceuticals, Inc. has submitted BLA 125390 seeking approval for the indication to treat metabolic complications of lipodystrophy, a rare disorder of leptin deficiency and loss of adipose tissue. Specifically, the PST will address the question of increased lymphoma risk.

Tumor surveillance requires an intact and balanced immune system. Lymphoma development has been associated with immune deficiency states, as well as over-stimulation or chronic inflammation as seen in autoimmune diseases (Stevens). Lymphomas develop in AIDS patients and patients with chronic Epstein Barr Viral infections. Autoimmune diseases, notably Systemic Lupus Erythematosus Lupus (SLE) and Sjogrens Syndrome/Sicca Syndrome, have been highly associated with lymphoma. Tumor necrosis factor (TNF) inhibitors have all been associated with the development of lymphomas. The exact mechanisms for these associations have not been fully elucidated. Current hypotheses are investigating altered immune balance as translated into T- and B-cell responses.

Obesity is a disease that produces chronic low-level inflammation. Leptin as an adipokine in preliminary work has been associated with lymphoma risk (Conroy). Adipokines act as cytokines that alter the immune response (Fantuzzi). Leptin promotes B-cell survival by protecting them from apoptosis and inducing cell-cycle entry via the induction of Bcl-2 and cyclin D1 (Lam). Leptin elevates Bcl-2 and cyclin D1 levels through at least two mechanisms, by activating their promoters and suppressing miRNAs that target the putative 3′untranslated regions (UTR) of Bcl-2 and cyclin D1 mRNAs.
Cytokines including leptin act on the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathways. JAK/STATs play a critical role in immune function and hematopoiesis (O'Shea). In humans, the JAK/STAT family consists of four JAK [JAK1, JAK2, JAK3, tyrosine kinase 2 (TYK2)] and seven STAT (STAT1,

STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6) proteins. This pathway has a central role in the signal transduction of cytokines by regulating cell proliferation, survival, and differentiation and therefore has an important role in oncogenesis (Vainchenker). Consequently, alterations may result in lymphomagenesis. Polymorphisms in JAK/STAT genes are associated with lymphomas (Chen, O'Shea). JAK/STAT proteins play an important role in regulating lymphoid homeostasis and immunity, including maintaining the balance between T-helper 1 (Th1) and Th2 T-cell response, the development of regulatory T (Treg) cells and the function of memory CD8+ cells (Derenzini, Quintas-Cardama). Specifically, gain in function mutations of JAK2 have been associated with a variety of lymphomas and therefore, JAK 2 inhibitors are being investigated for the treatment of relapsed lymphomas.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) approved a JAK STAT inhibitor, tofacatinib, in November 2012. Tofacatinib produces inhibition of JAK3 and JAK 1 with limited JAK2 inhibitory activity. Tofacatinib increased lipid levels in the clinical trials. Tofacatinib has a black box warning about cases of lymphoma.

Because of the central role of JAK/STAT signaling in the immune response, metreleptin may impact the development of immunogenicity, a common problem with biologics. However, it is unknown if an increased or decreased rate would be expected.

John O'Shea is referenced as a possible expert for an Advisory Committee meeting for metreleptin. He is from the NIH and did perform early work on JAK/STAT inhibition. A consult to DPARP is pending. This consult will likely address many of the points highlighted above and noted in his recent publication.
Additionally, MASE (Molecular Analysis of Side Effects) was queried to investigate JAK/STAT inhibition. While this protein target is in the database an adverse event profile is not yet available. The current structure activity program used by the Predictive Safety Team, SeaChange, analyzes small molecules and not biologics at this time.
In conclusion, leptin and consequently metreleptin, alter the delicate balance of the immune system. It is therefore possible that genetically predisposed individuals possibly with additional environmental exposures that require an immune response may have an increased risk for developing lymphoma. Please let the PST know how we can be of further assistance.

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/s/

JAYABHARATHI VAIDYANATHAN
11/15/2013

KEITH K BURKHART
11/15/2013

DARRELL R ABERNETHY
11/15/2013

IMMO ZADEZENSKY
11/15/2013

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**125390**	**Brand Name**	**Myalept**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Metreleptin**
Medical Division	**DMEP**	**Drug Class**	**Recombinant leptin analog**
OCP Reviewer	**Jayabharathi Vaidyanathan**	**Indication(s)**	Indicated for the treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy.
OCP Team Leader	**Immo Zadezensky**	**Dosage Form**	**Injection**
		Dosing Regimen	**Once daily**
Date of Submission	**3/27/2013**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCP Review	**11/27/13**	**Sponsor**	**Amylin**
PDUFA Due Date	**2/27/14**	**Priority Classification**	**Priority**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	5		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:		**1**		
multiple dose:		**1**		
Patients-				
single dose:				
multiple dose:		**1**		**Pk in a subset of Phase 3 trial FHA101**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

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Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**8**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The to-be-marketed product is the same as the formulation used in Phase 2 and Phase 3 trials
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Metreleptin is a biologic (147 aminoacids) and its metabolism is not mediated by Phase 1 and 2 drug metabolizing enzymes. There is no concern of drug-drug interaction.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			

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5	Has a rationale for dose selection been submitted?		X		
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic	X			

	requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Submission in Brief:

Background:

Amylin Pharmaceuticals, a subsidiary of BMS, has submitted a Biologics License Application (BLA 125390) for Myalept (metreleptin). The proposed indication is for the treatment of metabolic disorders associated with lipodystrophy including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy. There are currently no approved treatments for lipodystrophy and metreleptin has received Orphan Drug designation for this indication. BLA 125390 was submitted in different sections or modules under the "rolling review" program. The final reviewable unit was submitted on March 27, 2013. This application will be a priority review and will be discussed at an Advisory Committee meeting.

Metreleptin, a recombinant analog of human leptin, consisting of 147-amino acids that differs from the human leptin sequence by one additional amino acid, methionine, located at the amino-terminal end. Leptin is the product of the obese (*ob*) gene and is a naturally occurring hormone predominantly secreted by adipose tissue that plays a central role in the neurohormonal regulation of energy homeostasis and fat and glucose metabolism.

The sponsor's proposed dosing recommendation is shown in Table 1: Metreleptin is proposed to be administered by subcutaneous (SC) injection once daily (QD). Metreleptin is proposed to be administered into the SC tissue of the abdomen, thigh, or upper arm and may be alternated among these sites as needed depending on amount of SC tissue in these areas.

Table 1: Metreleptin Recommended Daily Dose by Weight and Gender

Baseline Weight	Daily Dose (Injection Volume)
≤40 kg (males and females)	0.06 mg/kg (0.012 mL/kg)
>40 kg	
Males	2.5 mg (0.5 mL)
Females	5.0 mg (1.0 mL)

Lipodystrophy is a group of very rare disorders that is characterized by generalized or partial loss of adipose tissue and leptin deficiency. In lipodystrophy patients, the profound deficiency of adipose tissue leads to accumulation of fat in the bloodstream (with resultant hypertriglyceridemia) and ectopic deposition of fat in non-adipose tissues such as liver and muscle, leading to metabolic abnormalities including insulin resistance and diabetes. By correcting leptin deficiency, metreleptin improves several of these metabolic abnormalities including diabetes and hypertriglyceridemia.

The metreleptin clinical development program for lipodystrophy in support of the BLA consisted of one completed study (NIH 991265) and 2 ongoing studies (NIH 20010769 and FHA101). The pivotal data for this BLA are based on 72 lipodystrophy patients treated with metreleptin from the two open-label, investigator-sponsored studies (completed study 991265 and ongoing study 20010769). Neither study had a placebo or comparator group. In addition to clinical experience with metreleptin in lipodystrophy, metreleptin has been administered to over 1,100 subjects (without lipodystrophy) in 15 clinical studies conducted as part of Amgen Inc's (Amgen) clinical development program of metreleptin monotherapy for obesity. In these studies, daily doses up to 30 mg have been administered.

Based on the results from the pivotal NIH trials (991265 & 20010769), metreleptin reduced fasting glucose, fasting triglycerides and HbA1c from baseline as shown in Table 1below.

Table 1: Change From Baseline Month 4, 8, and 12 in HbA1c, FPG, and Fasting TG (NIH; ITT Population Observed Data for Each Efficacy Parameter)

Parameter	Statistic [1][2]	Month 4	Month 8	Month 12
HbA1c (%)	**N**	45	51	50
	Baseline Mean (SD) [3]	8.3 (2.0)	8.4 (2.1)	8.2 (2.2)
	Change from Baseline			
	Mean (SE)	-1.1 (0.2)	-1.3 (0.2)	-1.4 (0.2)
	Median	-0.8	-1.1	-1.1
	Min, Max	-5.8, 1.8	-5.5, 1.3	-5.8, 0.9
	95% CI [4]	-1.6, -0.7	-1.8, -0.9	-1.8, -0.9
FPG (mg/dL)	**N**	46	54	52
	Baseline Mean (SD) [3]	192.1 (86.6)	176.3 (86.1)	169.9 (88.5)
	Change from Baseline			
	Mean (SE)	-45.5 (11.6)	-34.2 (9.9)	-41.8 (11.7)
	Median	-38	-26	-26
	Min, Max	-311, 125	-216, 165	-232, 271
	95% CI [4]	-68.8, -22.1	-54.0, -14.3	-65.2, -18.4
Fasting TG (mg/dL)	**N**	45	52	51
	Baseline Mean (SD) [3]	959.3 (1331.1)	1174.8 (2377.6)	1015.7 (1780.3)
	Change from Baseline			
	Mean (SE)	-472.1 (172.3)	-584.6 (285.1)	-672.9 (223.4)
	Median	-188	-58	-121
	Min, Max	-5682, 2811	-10377, 4345	-8866, 521
	Percent Change from Baseline			
	Mean (SE)	-38.0 (5.9)	-10.5 (9.4)	-31.9 (7.6)
	Median	-42.6	-23.4	-44.8
	Min, Max	-93.9, 94.2	-91.8, 287.7	-93.3, 194.4
	95% CI [4]	-49.9, -26.2	-29.4, 8.4	-47.2, -16.6

CI = confidence interval; SD = standard deviation; SE = standard error; min = minimum; max = maximum.

[1] N at each time point represents ITT patients with data for the key efficacy parameter at baseline and
[2] N at the same time point may vary across efficacy parameters (i.e., HbA1c, FPG, and TG) as it is dependent on the number of patients with an available value for that specific parameter. the specified visit.
Given the nature of this ongoing, open-ended, investigator-sponsored study, N may vary at each visit due to inter-patient variability in duration of exposure and frequency of visits, as well as patient discontinuation from the study.
[3] In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin and is calculated for those patients with values at the specified visits.
[4] 95% confidence interval from paired t-test.
Note: Mean/median change was calculated from the changes for all ITT patients with values at baseline and at the given visits.

Pharmacokinetic (PK): There are limited data on PK of metreleptin in lipodystrophy patients and therefore no exposure-response has been performed. The disposition of metreleptin has been quantified in two clinical trials in healthy subjects as part of Amgen's prior clinical development program in obesity. The PK properties of metreleptin in lipodystrophy patients were assessed in a subset of patients from study FHA101. Plasma concentrations of total leptin (endogenous leptin plus metreleptin) from two NIH studies were also used to summarize the exposure of metreleptin in lipodystrophy patients.

Table 2 shows the summary of PK parameters of metreleptin in healthy subjects. It should be noted that the leptin assay measures both endogenous leptin as well as exogenously administered metreleptin. In these healthy adults when metreleptin was administered via intravenous and SC route, the absolute bioavailability was approximately 94% using doses of 0.3 to 3.0 mg/kg/day. Peak serum leptin concentrations occurred around 4 h after SC administration. There was no accumulation of metreleptin upon multiple intravenous injections for 15 days. The half-life was found to be between 3-4 h in these studies.

Table 2:

Mean (SD) Non-Compartmental Pharmacokinetic Parameters by Dose Group Day 1 in Healthy Subjects Across a Range of BMIs (Study LEPT-970121 and Study LEPT-950272)

Study	LEPT-970121 (IV)			LEPT-950272 (SC)	
Study Day	Day 1			Day 1	
Dose Group (mg/kg)	0.3	1.0	3.0	0.1	0.3
N	27	14	12	31	26
C_{avg} (ng/mL)	162.1 (30.8)	521.1 (100.5)	1361.2 (299.3)	—	—
T_{max} (hr)	—	—	—	4.3 (1.5)	4.0 (1.5)
C_{max} (ng/mL)	6160.0 (1385.9)	17582.0 (2913.8)	32887.3 (4976.2)	119 (32)	343 (104)
nC_{max} (ng/mL/mg/kg)	20533.4 (4619.6)	17582.0 (2913.8)	10962.4 (1658.7)	1190 (320)[a]	1143 (347)[a]
$t_{½}$ (hr)	3.34 (1.88)	3.41 (0.85)	3.42 (0.82)	4.3 (2.7)	3.8 (1.4)
$AUC_{0-\infty}$ (ng*hr/mL)	3908.8 (754.1)	12544.7 (2449.2)	32775.7 (7250.7)	1180 (267)	3657 (781)
AUC/D (ng*hr/mL/mg/kg)	13029.3 (2513.7)[a]	12544.7 (2449.2)[a]	10925.2 (2416.9)[a]	11800 (2675)	12190 (2603)
CL (mL/kg/hr)	79.6 (16.1)	82.5 (15.6)	95.8 (21.6)	89 (20)	86 (18)
Vz (mL/kg)	370 (184)	398 (92)	463 (116)	519 (276)	444(117)

[a] Derived from values provided in this table.

In NIH pivotal studies 991265/20010769, increases in mean (SE) fasting serum leptin concentrations (from baseline concentrations of 2.8 [0.39] ng/mL) to moderately supraphysiologic concentrations were observed at month 4 following metreleptin treatment (18.6 [2.7]) ng/mL and maintained throughout the entire treatment period. Mean fasting serum leptin concentrations in the 20-ng/mL to 30-ng/mL range were generally achieved over the entire treatment period.

There were no formal drug-drug interaction, renal impairment, hepatic impairment or other PK studies conducted to address the effect of intrinsic/extrinsic factors on metreleptin PK. Because metreleptin is primarily cleared by the kidney, the PK of metreleptin may be altered in subjects with renal impairment, but hepatic dysfunction is not expected to affect the PK of metreleptin.

No thorough QT (TQT) study was conducted with metreleptin. The applicant has submitted a TQT waiver request. QT-IRT has been consulted regarding this request.

Formulation: (b) (4) A lyophilized formulation was developed and used in clinical trials and is the proposed commercial formulation.

Table 3: Metreleptin Drug Product Formulations Used in Clinical Studies

Dosage Form	Metreleptin Concentration	Composition	Clinical Phase[a]
(b) (4)			
Lyophilized	5.0 mg/mL	(b) (4) glutamic acid, (b) (4) glycine, (b) (4) sucrose, (b) (4) polysorbate 20, pH 4.25	2 and 3, Proposed Commercial

[a] A list of clinical studies and the formulation used in each study is provided in Section 2.3.P.5.4, Batch Analyses (Metreleptin, Injection) (b) (4)

Reviewer Comments:

- At the time of last submission in 2012, the sponsor did not submit the complete study reports for the PK studies that were being used to support labeling claims regarding bioavailability of metreleptin. Information request was sent to the sponsor to provide these study reports. The sponsor has submitted these study reports in this submission.
- Lack of the drug-drug interaction as well as metabolism studies were also not considered as filing issue since metreleptin is a biologic with no contribution of systemic metabolism and no potential of drug interaction.
- The metreleptin formulation that was used in the lipodystrophy clinical trials is the same as the to-be-marketed formulation.
- The application is fileable from clinical pharmacology.
- Review focus
  - What are the PK characteristics of metreleptin in lipodystrophy patients?
  - Is the proposed dose acceptable?
  - Is the metreleptin bioanalytical assay/validation acceptable?

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/s/

JAYABHARATHI VAIDYANATHAN
05/01/2013

IMMO ZADEZENSKY
05/02/2013