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APPLICATION NUMBER:

125390Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number	125390
Priority or Standard	Priority
Submit Dates	15 Dec 2010, 2 Apr 2012, 27 Mar 2013 (rolling)
Received Dates	same
PDUFA Goal Date	24 February 2014
Division / Office	DMEP / ODE2
Reviewer Name	Julie K. Golden, M.D.
Review Completion Date	(Addendum) 23 Feb 2014
Established Name	Metreleptin
Proposed Trade Name	Myalept
Therapeutic Class	Recombinant leptin analog
Applicant	Amylin Pharmaceuticals, LLC (Bristol-Myers Squibb Company)
Formulation	Injectable (when lyophilized cake reconstituted in BWFI or SWFI)
Dosing Regimen	Once daily
Indication	Treatment of complications of leptin deficiency
Intended Population	Patients with congenital or acquired generalized lipodystrophy

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the application be approved, with a modification of the indication to treat the complications of leptin deficiency in patients with generalized lipodystrophy.

It is my opinion that the indication should not include partial lipodystrophy for the following reasons:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

1.2 Risk Benefit Assessment

Leptin is an adipose tissue-derived hormone that plays a key role in energy homeostasis. Patients with lipodystrophy have varying degrees of fat loss (generalized

versus partial) and therefore varying degrees of leptin deficiency. The lack of adequate storage depots for fat in patients with lipodystrophy leads to its ectopic deposition in tissues such as muscle and liver, which results in metabolic diseases such as insulin-resistant diabetes mellitus, hypertriglyceridemia, and hepatic steatosis. Hyperphagia in these patients likely exacerbates metabolic disease. Replacement or supplementation of leptin with metreleptin appears to improve the metabolic complications of lipodystrophy, although importantly, it does not treat the underlying disorder.

Patients with generalized forms of lipodystrophy appear to achieve the best results with metreleptin treatment, including large and, in some cases, sustained improvements in HbA1c and TG, often accompanied by a discontinuation or decrease of anti-hyperglycemic or lipid-lowering therapies.

By contrast, patients with partial forms of lipodystrophy have a more varied, attenuated, and confounded response. There may be a subset of patients with partial lipodystrophy with very low leptin concentrations and significant metabolic disease that responds to metreleptin, although study design issues, confounders, and missing data presented review challenges that were very difficult to overcome in determining an appropriate subpopulation for treatment.

It is important to ensure that the appropriate patient population is targeted, given the serious risks that may be associated with the drug. Lymphoma and immunogenicity are risks that have been identified at this time; however, given the potential effects of leptin on a variety of organs and cellular functions, the potential for additional risks is theoretically possible.

With respect to lymphoma, although patients with acquired forms of lipodystrophy may be predisposed to developing lymphoma, it is biologically plausible that metreleptin could act as a cancer promoter. It is unknown whether metreleptin had any role in the development of T-cell lymphoma in the three patients with lymphoma in the NIH trial; however, it is also unclear if there is any way to mitigate this risk (e.g., avoiding use in patients with hematologic abnormalities prior to treatment), given that one of the three patients had no identified risk factors, aside from AGL.

In the lipodystrophy population, the risk of the development of neutralizing antibodies includes lack of efficacy and decrease in activity of endogenous leptin. Even in a leptin-deficient population characterized by low levels of circulating leptin but with normal leptin gene alleles, leptin made by immune cells could be sufficient in the microenvironment to activate immune cells in an autocrine or paracrine fashion; it is theoretically possible that circulating neutralizing antibodies could attenuate this action. Lipodystrophy, unlike congenital leptin deficiency, has not been described to be associated with impaired immune responses. However, at least one patient with generalized lipodystrophy and high-titer neutralizing antibodies has been described to be hospitalized with numerous bacterial infections. Although this patient had a number

of confounding risk factors for bacterial infections, the potential risk remains a significant concern.

The risk of developing a congenital leptin deficiency-like syndrome in non-leptin-deficient populations (which may include some forms of partial lipodystrophy) is significant. Three patients from an obesity program have been identified as having developed neutralizing antibodies in association with low leptin concentrations and excessive body weight increases. Given the interest in obesity therapies, ensuring that only the patient population that has been clearly identified as benefiting from metreleptin has access to the drug should be the goal of a risk evaluation and mitigation strategy (REMS). In the post-marketing setting, monitoring patients for the development of neutralizing antibodies, in addition to monitoring for benefit, could be considered as potential strategies to improve the benefit-to-risk relationship.

Therefore, based on the assessment of benefits and risks in the generalized and partial lipodystrophy populations, I recommend that this application be approved for the generalized lipodystrophy patient population. The indication should be modified to ensure that metreleptin is being used to treat the complications of leptin deficiency in this disease, (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Because of the risks of neutralizing antibodies and lymphoma as described above, metreleptin will be approved with a REMS with elements to assure safe use (ETASU). Elements will include:

- Prescriber certification
- Pharmacy certification
- Documentation of safe use conditions through prescriber attestation: prescribers will attest that they understand the indication, limitations of use, contraindication, and potential risks

1.4 Recommendations for Postmarket Requirements and Commitments

Seven PMRs and eight PMCs will be conveyed to the company. PMRs are as follows:

- PMR 1: A long-term prospective observational study (product exposure registry) of patients treated with Myalept (metreleptin), regardless of indication), to evaluate serious risks related to the use of Myalept (metreleptin), by indication, including: fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, serious infections resulting in hospitalization or death,

new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, lymphoma, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes, and all deaths (including causes of death).

- PMR 2: To develop, validate, and implement a ligand binding assay to supplement the neutralizing bioassay that tests for the presence of neutralizing antibodies in serum samples from patients with generalized lipodystrophy.

- PMR 3: To test all banked clinical samples from NIH 991265/20010769 and FHA101 trials for the presence of neutralizing antibodies against leptin using the ligand binding assay developed and validated under PMR 2, and to correlate neutralizing antibodies with clinical events.

- PMR 4: To conduct a study to assess for the immunogenicity of Myalept (metreleptin) in a relevant number of patients receiving metreleptin. The study should include testing for anti-metreleptin and anti-native human leptin binding antibodies at times when antibody responses peak, using a validated assays. The presence of neutralizing antibodies should be assessed using a validated cell-based assay and a validated ligand-binding assay in samples that are confirmed positive for binding antibodies to leptin. All patients with suspected loss of metreleptin efficacy (e.g., worsening glycemic control, increases in triglycerides) or loss of endogenous leptin activity (e.g., severe infections) should be tested for neutralizing activity and followed at least until antibody levels revert to baseline. Antibody titers, neutralizing activity, and associated clinical events should be characterized over time.

- PMR 5: An assessment and analysis of spontaneous reports of serious risks related to the use of Myalept (metreleptin) including: fatal or necrotizing pancreatitis, hepatic adverse events, severe hypoglycemia, serious hypersensitivity reactions, serious infections resulting in hospitalization or death, new diagnoses of autoimmune disorders (for instance, autoimmune hepatitis, glomerulonephritis, lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis), autoimmune disease exacerbation, all cancers (excluding non-melanoma skin cancer) by cancer type, exposed pregnancies and pregnancy outcomes, and all deaths (including causes of death) in patients treated with Myalept (metreleptin) regardless of indication for 10 years from the date of approval.

- PMR 6: To determine the approximate percent of potential impurities derived from the *E. coli* cell line used to manufacture metreleptin that are detected by the ELISA to assess for host cell proteins (HCP) in metreleptin drug substance using a sensitive and discriminating assay such as 2D gel electrophoresis to detect impurities that can lead to increased immunogenicity.

- PMR 7: To confirm the in-use stability of metreleptin drug product (DP) reconstituted in bacteriostatic water for injection containing 0.9% benzyl alcohol (BFWI) with data derived from three additional DP lots, to assess aggregate formation which can impact immunogenicity.

2 Introduction and Regulatory Background

Lipodystrophy

Lipodystrophy is a group of very rare disorders that is characterized by generalized or partial loss of adipose tissue. A recent review[1] estimates 1350 cases of lipodystrophy have been reported worldwide (approximately 1000 patients with inherited forms of lipodystrophy and 350 patients with acquired forms excluding human immunodeficiency virus (HIV)-related lipodystrophy). Based on an assumption that only one fourth of patients are reported, the prevalence of genetic forms of lipodystrophy in the general population has been estimated at less than one in a million. In patients with lipodystrophy, the profound deficiency of adipose tissue leads to accumulation of fat in the bloodstream and ectopic deposition of fat in non-adipose tissues such as liver and muscle, which results in hypertriglyceridemia and insulin resistance. The extent of fat loss often correlates with the severity of the metabolic complications;[1] some patients with lipodystrophy have associated co-morbidities such as diabetes mellitus, pancreatitis, and hepatic steatosis,[2] whereas other patients may have less severe metabolic complications, but significant aesthetic concerns.[3] Many patients require multiple medications to manage their diabetes and/or hypertriglyceridemia.

Lipodystrophy is generally classified as congenital/familial or acquired, and generalized or partial. Therefore, lipodystrophy subtypes will often be referred to in this review as congenital generalized lipodystrophy (CGL), acquired generalized lipodystrophy (AGL), familial partial lipodystrophy (FPL), and acquired partial lipodystrophy (APL). However, within subtypes there may be differences in clinical presentation, and given the ongoing understanding of the underlying genetic basis of disease or progression of fat loss over time, a particular patient's classification may change in the future. Nevertheless, it serves as a useful guide to assessing the risks and benefits of potential therapies, such as metreleptin. Note that HIV-associated lipodystrophy (a form of acquired partial lipodystrophy) is beyond the scope of this review, as patients with this condition were not studied in this development program.

The various subtypes of lipodystrophy have been reviewed; the following is summarized from references 1 and 2:

- Congenital generalized lipodystrophy (CGL) is also known as the Berardinelli-Seip syndrome. CGL is characterized by a nearly complete absence of adipose tissue and a generalized muscular appearance recognized easily at birth. Severe

hyperinsulinemia and hypertriglyceridemia may be present, even during infancy. Extreme hypertriglyceridemia may result in recurrent acute pancreatitis. Patients present with accelerated linear growth, an advanced bone age, and a voracious appetite in early childhood. Over time, patients develop diabetes mellitus and hepatomegaly. Nonalcoholic steatohepatitis may ultimately lead to cirrhosis. After puberty, clitoromegaly and the polycystic ovary syndrome may develop in girls. Only a few affected women have had successful pregnancies[*], whereas affected men have normal fertility. Known genes associated with CGL and the described phenotypes are listed below[†]:

Table 1. CGL Subtypes

Subtype (gene)	Key clinical features	Molecular basis
CGL1 (*AGPAT2*)	Lack of metabolically active adipose tissue since birth	AGPATs are key enzymes required for triglyceride and phospholipid biosynthesis. AGPATs acylate lysophosphatidic acid to form phosphatidic acid. AGPAT2 is highly expressed in adipose tissue.
CGL2 (*BSCL2*)	Lack of both metabolically active and mechanical adipose tissue since birth, mild mental retardation, cardiomyopathy	*BSCL2* encodes seipin, which may play a role in fusion of small lipid droplets and in adipocyte differentiation.
CGL3 (*CAV1*)	Single patient with extreme loss of body fat, short stature, and vitamin D resistance	Caveolin 1 is an integral component of caveolae, present in abundance on adipocyte membranes. Caveolin 1 binds fatty acids and translocates them to lipid droplets.
CGL4 (*PTRF*)	Extreme lack of body fat, congenital myopathy, pyloric stenosis, and cardiomyopathy	PTRF (also known as cavin) is involved in biogenesis of caveolae and regulates expression of caveolins 1 and 3.

Source: Reference 1

- The fat loss with AGL occurs during childhood and adolescence and particularly affects the face, arm, and legs. Subcutaneous fat may also be lost from the palms and soles, while retro-orbital and bone marrow fat may be preserved. The degree of loss of intra-abdominal fat varies. Affected children may have a voracious appetite. Acanthosis nigricans and hepatic steatosis also develop in most patients beginning in childhood. AGL patients often develop hepatic fibrosis, diabetes, and hypertriglyceridemia. The pathogenesis of fat loss in patients with AGL is variable. AGL can be associated with panniculitis (25%), autoimmune diseases such as juvenile dermatomyositis (25%), and in addition, an idiopathic variety has been described (50%). Patients with panniculitis present with adipose tissue infiltrated with histiocytes, lymphocytes, and multinucleated giant cells, together with a granulomatous reaction. These lesions progress from localized loss of subcutaneous fat to loss of fat from almost all subcutaneous regions, eventually causing generalized lipodystrophy.

[*] Note that 3 out of 4 pregnancies reported in the metreleptin lipodystrophy development program occurred in women who had a CGL diagnosis
[†] Note that genotype information for the patients in the lipodystrophy trials that support the BLA was not provided to FDA.

- Familial partial lipodystrophies (FPL) are heterogeneous, autosomal dominant disorders with several distinct phenotypes (see the table below). The most prevalent is the Dunnigan variety, which is associated with mutations in the lamin A/C gene (*LMNA*).[4] The distribution of body fat is normal during childhood, but with puberty, subcutaneous fat gradually disappears from the arms and legs, resulting in a muscular appearance. Variable and progressive loss of fat from the anterior abdomen and chest occurs later. Many patients, particularly women, gain fat in the face, neck, and intraabdominal region, resulting in a cushingoid appearance. Acanthosis nigricans and the polycystic ovary syndrome are relatively uncommon. The diagnosis is reported to be relatively easy to make in women, but is difficult in men, since many normal men have a muscular habitus. Whole-body magnetic resonance imaging reveals subcutaneous fat loss but increased intermuscular fat in the arms and legs and excess intraabdominal fat. Diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, and atherosclerotic vascular disease are more prevalent in female patients than in male patients. Diabetes usually develops after the second decade of life, associated with multiparity and excess fat in nonlipodystrophic regions in affected women. Marked hypertriglyceridemia has been associated with acute pancreatitis. Although fatty liver occasionally develops, cirrhosis has not yet been reported in these patients.

Table 2. FPL Subtypes

Subtype (gene)	**Key clinical features**	**Molecular basis**
FPLD1, Kobberling (unknown)	Loss of subcutaneous (sc) fat from the extremities	Phenotype not well characterized.
FPLD2, Dunnigan (*LMNA*)	Loss of sc fat from the extremities and trunk (sparing the face and neck) at puberty	Lamins A and C are nuclear lamina proteins and specific mutations may disrupt nuclear function resulting in premature death of adipocytes.
FPLD3 *(PPARG)*	Loss of sc fat from the extremities, especially from distal regions	PPARγ is a critical transcription factor required for adipogenesis. Dominant negative PPARγ mutations may inhibit adipocyte differentiation.
FPLD4 (*AKT2*)	Single family reported with loss of sc fat from the extremities	AKT2, also known as protein kinase B, is involved in adipocyte differentiation and downstream insulin receptor signaling.
FPLD5 (*PLIN1*)	Loss of sc fat from the extremities with small adipocytes and increased fibrosis of adipose tissue	Perilipin 1 is an integral component of lipid droplet membranes and is essential for lipid storage and hormone regulated lipolysis.
Unnamed FPL subtype (*CIDEC)*	Single patient with loss of sc fat from limbs, multilocular, small lipid droplets in adipocytes	CIDEC is a lipid droplet associated protein that inhibits lipolysis and promotes formation of unilocular lipid droplet in adipocytes.

Source: Reference 1

- APL not associated with HIV infection is known as the Barraquer-Simons syndrome. The fat loss occurs during childhood or adolescence, affecting the face, neck, arms, thorax, and upper abdomen in a cephalocaudal fashion. Excess fat may be

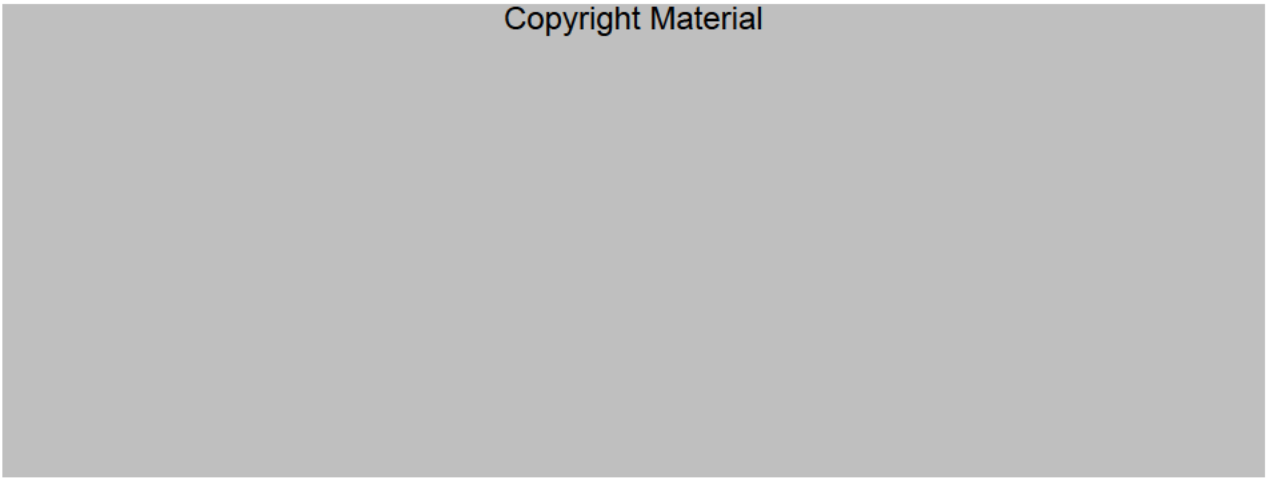
deposited in hips and legs. Insulin resistance is infrequent.‡ Patients have low levels of serum C3 accompanied by detectable levels of C3 nephritic factor. C3 nephritic factor–induced lysis of adipocytes may be involved in the pathogenesis of this form of lipodystrophy. It is also associated with other autoimmune conditions. Membranoproliferative glomerulonephritis has been reported in approximately 20 percent of patients.

Leptin (Reviewed in Reference 5)

Leptin in humans and other mammalian species is the protein product of the *ob* gene. Leptin is a 146-amino acid protein synthesized primarily in white adipose tissue, and is homologous in structure to a cytokine. Secreted leptin acts on hypothalamic feeding centers in the brain, signaling the energy stores of the body (e.g., low fat stores in starvation decrease circulating leptin, leading to an increase of energy intake).

Circulating leptin concentrations strongly correlate with body fat stores. In one paper, mean serum leptin concentrations in 139 obese individuals was 31.3 ± 24.1 ng/mL, as compared with 7.5 ± 9.3 ng/mL in 136 normal-weight individuals ($p < 0.001$).[6] Leptin concentrations are greater in females compared to males, and some authors have found this to be true even when correcting for differences in body composition,[7,8] while others have not.[6] The third National Health and Nutrition Examination Survey conducted in 6303 women and men aged 20 years or older reported the mean serum leptin concentration in women to be 12.7 ng/mL and in men 4.6 ng/mL.[9] (See the table from this publication below, which provides leptin concentrations by sex and race/ethnicity.) Leptin concentrations fall and rise, respectively, with short-term fasting and refeeding,[10] although leptin does not appear to rise acutely after individual meals.[11]

Table 3. Range of Leptin Concentrations in Adults



Source: Reference 9

‡ This may explain why there are few patients with APL in the metreleptin program.

Leptin receptors are members of the class I cytokine receptor family and have multiple isoforms, with identical extracellular ligand binding domains and varying lengths of intracellular domains for signal transduction.[12] In addition to its effects on energy homeostasis, leptin and its receptors appear to serve an important role in inflammation, via activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway,[13] and reproduction.[14]

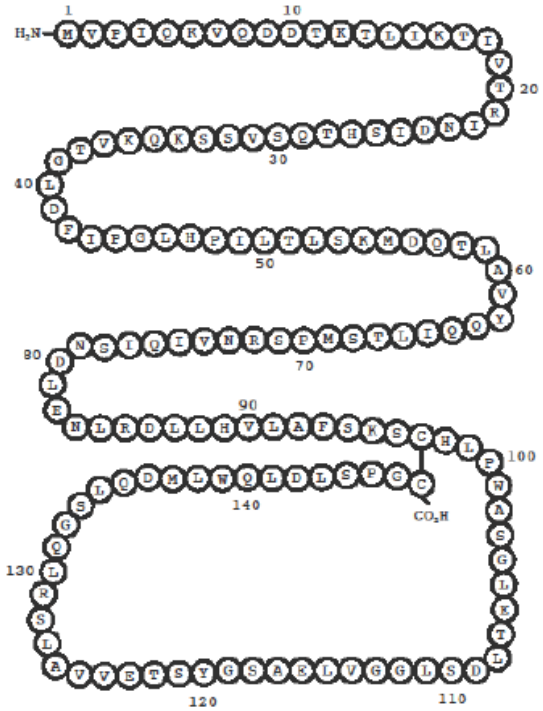
2.1 Product Information

The new molecular entity (NME), metreleptin, is a recombinant analog of the endogenous human hormone, leptin. The proposed tradename is Myalept.

Metreleptin is a 147 amino acid, non-glycosylated polypeptide with one disulfide bond. It has the empirical formula $C_{714}H_{1167}N_{191}O_{221}S_6$ and a molecular weight of approximately 16.2 kDa. Metreleptin differs from the human leptin sequence by one additional amino acid, methionine, located at the amino-terminal end.

The amino acid sequence and structure for metreleptin is shown in the following figure.

Figure 1. Metreleptin Structure



Source: BLA 125390 3.2.S.1.2, Figure 1

The proposed indication is as follows:[§]

MYALEPT (metreleptin for injection) is a recombinant analog of human leptin indicated for the treatment of pediatric and adult patients with:

- *Generalized lipodystrophy.*
- *Metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis.*

2.2 Currently Available Treatments for Proposed Indications

There are no approved drugs specifically for the treatment of metabolic disorders associated with lipodystrophy. Currently available treatments for this orphan population are directed toward addressing the individual metabolic abnormalities, and can include insulin and oral hypoglycemic agents for insulin resistance and diabetes, and statins, fibrates, niacin, and fish oil for hypertriglyceridemia. Decreasing caloric intake can also improve metabolic disorders associated with lipodystrophy.

2.3 Availability of Proposed Active Ingredient in the United States

Metreleptin is only available as an investigational medication in the U.S.

2.4 Important Safety Issues with Consideration to Related Drugs

Not applicable. There are no other related drugs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following table summarizes the metreleptin regulatory history. Metreleptin has been studied for treating lipodystrophy-related conditions since 2000.

Table 4. Metreleptin Regulatory History

Date	Activity
16 May 2001	Amgen EOP2 meeting with the Agency (IND 50259) • The Division agreed that study 991265 (8-month initial trial in 9 patients) was sufficient to use as the single pivotal trial in a leptin NDA • The Division suggested that the NDA could be strengthened by following patients during a drug withdrawal and re-treatment period • Concern about off-label use was raised; there was discussion about whether this could be addressed through restricted distribution • The sponsor noted that dose and schedule were developed to achieve replacement levels of leptin, but that triglyceride (TG) and glucose levels, rather than leptin levels, were used to

[§] Revised 5 Nov 2013

Date	Activity
	titrate the drug • The Division indicated that dosing rationale should be included in the NDA • The Division agreed that sufficient data exist from studies 991265 and 970161 [study in primary leptin deficiency] to support use in pediatric patients • The Division concurred that the safety package consisting of the obesity and diabetes trials conducted with metreleptin would provide sufficient safety data to support the NDA, and that these data could be submitted as an ISS without individual study reports • The Division stated that the indication should identify the disease population and benefits expected with the drug • FDA could not state what the review status (i.e., priority vs. standard) would be at this time • The preclinical program is adequate for the narrow indication/population
22 Aug 2001	Amgen was granted orphan designation of metreleptin for the treatment of metabolic disorders secondary to lipodystrophy (OD 01-1467)
22 Oct 2001	Amgen was granted fast track designation of metreleptin for the treatment of metabolic disorders associated with lipodystrophy
03 Mar 2006	Amylin assumed sponsorship of metreleptin (IND 50259) from Amgen Amylin assumed ownership of Amgen's metreleptin inventory manufactured at 2 sites (Thousand Oaks and Lake Centre) and Amgen's master and working cell banks
17 Oct 2007	Type C meeting convened to confirm Amylin's interpretation of Amgen's EOP2 meeting in 2001 and to obtain DMEP's guidance related to updated clinical and nonclinical data for lipodystrophy • Clinical package of 29 patients from NIH trials sufficient • Non-clinical package sufficient • HIV-related lipodystrophy not within the scope of the proposed indication
01 May 2008	CMC IND amendment filed to add Sandoz GmbH (Kundl, Austria) as an additional manufacturer of drug substance
19 May 2008	Treatment IND 101824 filed as means to expand access to metreleptin for patients with metabolic disorders associated with lipodystrophy until submission of the NDA Sandoz GmbH is proposed as an additional drug substance manufacturer for the treatment IND
05 Jun 2008	Teleconference with FDA to discuss using Sandoz drug substance in the treatment IND
08 Jun 2008	FDA authorized the "Treatment IND May Proceed", but only using Amgen drug substance for clinical use FDA indicated that additional work needed to be performed in order to establish comparability between Sandoz and Amgen drug substance, including a 28-day bridging toxicology study
Feb 2009	FDA was notified about 2 cases of peripheral T cell lymphoma that occurred in the lipodystrophy program (IND 60534); in response, Amylin: • Amended the exclusion criteria of the treatment protocol FHA101 (IND 101824) to exclude those patients with acquired lipodystrophy who have clinically significant hematologic abnormalities, such as neutropenia and/or lymphadenopathy • Notified all investigators and physicians who are involved in lipodystrophy clinical trials and compassionate use treatments with metreleptin of these reports of peripheral T-cell lymphoma and assessment of these cases
10 Sep	Amylin provided additional CMC and nonclinical information on metreleptin to qualify Sandoz GmbH as a drug substance manufacturer and to seek agreement that Sandoz drug substance is

Date	Activity
2009	suitable for clinical use
22 Oct 2009	Request for comments: Amylin proposed filing the lipodystrophy NDA with Amgen drug substance because of its long history of clinical use without apparent safety concerns and continuing stability and based on the large quantity of Amgen drug substance available to supply metreleptin for this small orphan population for the foreseeable future
10 Dec 2009	FDA response indicating lack of concurrence that comparability had been fully established between Amgen and Sandoz metreleptin material by the CMC characterization information provided. FDA recommended against an NDA filing with Amgen drug substance, despite its use to supply the ongoing treatment protocol in lipodystrophy. The lack of a site for pre-approval inspection categorized the Amgen drug substance as out of compliance with Agency policy.
08 Feb 2010	Amgen communicated an intention to file the metreleptin for lipodystrophy NDA with Sandoz material To expedite availability of this orphan designated drug, Amylin submits "Request for Submission of Portions of an Application" (i.e., rolling review)
02 Apr 2010	Amylin requested a teleconference with the chemistry reviewer to clarify the scope of the Agency's information requests to facilitate transparency and ensure submission of the appropriate information and data
09 Apr 2010	Agency issued advice/information request for a briefing book and meeting to discuss the development proposal and the following specific issues: • Amylin's plans for sourcing drug substance and drug product • Possible alternative scenarios if drug substance from the proposed new drug manufacturer, Sandoz GmbH, cannot be qualified as comparable to material manufactured by Amgen • The need for additional clinical and nonclinical information if the Sandoz material is not comparable • Amylin's plans for use of Amgen material and Sandoz drug substance within a single NDA • Details on the status and projected timeline for each portion of the lipodystrophy NDA
30 Jul 2010	Agency's acceptance of rolling submission timeline and plans
13 Oct 2010	Letter states that per the Patient Protection and Affordable Care Act the Agency now believed that the appropriate marketing application for metreleptin is a BLA
18 Oct 2010	Agency's acceptance of chemical comparability of the Sandoz material
22 Oct 2010	Amylin submitted a request for Agency's comments regarding Amylin's proposed filing strategy for the CMC portion of the rolling BLA submission, a strategy that would allow compliance with the agreed upon rolling submission schedule
16 Nov 2010	Results of the 1-month toxicology study in mice adequately bridge the Sandoz-sourced metreleptin to the non-clinical data available for the Amgen sourced metreleptin. The non-clinical data support initiation of clinical studies with the Sandoz-sourced metreleptin. Amylin was asked by FDA to collect anti-leptin antibody data on patients transitioned to as well as those naïve to Sandoz metreleptin and include that information in the BLA safety update.
15 Dec 2010	Clinical and non-clinical modules submitted along with draft product label Clinical module included: NIH trials: N=55 patients; FHA101 trial: N=10 patients
03 Feb 2011	Agency requested an assessment of comparability between the Sandoz 2000 L DS and Sandoz 1000 L materials
May 2011	Meeting with Amylin to discuss 2 patients in the obesity program (IND 50259) with neutralizing antibodies to leptin and excessive weight gain
01 Apr	Submission of Module 3 including data to establish comparability between Sandoz DS made at

Date	Activity
2012	2 different fermentation scales. The submission also included: • Clinical Addendum to provide clinical experience with Sandoz DS focusing on Amylin's assessment of the immunogenicity of metreleptin manufactured at Sandoz in comparison with metreleptin manufactured at Amgen • Proposed RMP • Updated draft labeling
30 May 2012	Discuss the completeness of the BLA As studies were still ongoing and enrolling patients, the Agency conveyed that there were additional evaluable data from patients who had enrolled in these studies after the datacuts of the original Dec 2010 submission and that such data should be included in the BLA at the time of filing
June 2012	Amylin submitted non-clinical and CMC information amendments to IND 101824, in order to begin dosing patients using metreleptin manufactured at Sandoz at the 1000L scale
11 Jul 2012	Amylin and Agency had a teleconference to agree on the information/data to complete the BLA • Agency specifically requested additional efficacy and safety analyses as well as a comprehensive assessment of immunogenicity (lipodystrophy and obesity)
22 Jul 2012	FDA requested additional analyses and specific format for data presentation for Summary of Clinical Safety update, Summary of Clinical Efficacy update, and Clinical Addendum
Aug 2012	FDA informed of a 3rd patient in the obesity program (IND 50259) with neutralizing Abs to leptin and excessive weight gain
23 Oct 2012	Agency recommended Amylin request a pre-BLA meeting prior to submission as outlined under PDUFA V's "The Program"
30 Nov 2012	The Agency received an email from Amylin indicating there may be a possible shortage of metreleptin due to delays in manufacturing of drug product and a shortage of bacteriostatic water for injection (BWFI)
05 Dec 2012	Type A meeting: Discussed the manufacture and clinical use of metreleptin for lipodystrophy Because of possible drug shortage, the company contacted investigators and asked them to stop enrolling any new patients
17 Dec 2012	Pre-BLA meeting: • Agreements confirmed with regard to outstanding clinical documents/data to complete the BLA filing (NIH trials N = 72; FHA101 trial N=28) • Non-clinical information was also confirmed • RMP adequate to mitigate for risks now • A potential exists for a REMS request during review as noted in the preliminary response from FDA • Clarification was received for the 2013 manufacturing campaign
2 Jan 2013	The Agency requested additional information to be submitted with the final section of the BLA in order to facilitate the OSI development of clinical investigator and sponsor/monitor/contract research organization inspection assignments
Jan 2013	FDA informed of 3rd patient in the lipodystrophy program (IND 60534; NIH trials) diagnosed with lymphoma
22 Jan 2013	FDA requested lymphoma case analysis and update to Investigator's Brochure and all informed consent forms to include available information about lymphoma in metreleptin-treated patients
29 Jan 2013	FDA provided advice on performing in-process intermediate hold time study
1 Feb 2013	Agency requested a status update on obtaining BWFI for use with metreleptin

Date	Activity
26 Feb 2013	Amylin submitted a response stating that they do not anticipate any shortage of BWFI as the supply has been secured for the duration of 2013
27 Feb 2013	FDA requested breakdown of clinical data from 11 Jul 2011 / 07 Mar 2012 cutoffs (N=100) and Jan 2013 cutoff (N = 125, 4-month safety update) by sex and lipodystrophy subtypes [for oncology consultant] FDA requested estimated date for submission of the last BLA module
27 Mar 2013	BLA submitted • Updated labeling • Updated risk management plan • CMC data • Updated clinical data

Source: BLA 125390, Section 2.5 Clinical Overview Appendix 3, date 27 Mar 2013; internal FDA files

2.6 Other Relevant Background Information

Metreleptin received marketing approval in Japan on 25 Mar 2013 for treatment of lipodystrophy.[15]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There is no evidence to suggest that the investigators who were involved in treating patients with metreleptin, nor the sponsor, conducted the trials and the analyses with anything but good intent. Nevertheless, there are a number of limitations to these trials that call into question the validity of some results. Furthermore, given the nature of the disease (rare, with heterogeneous presentation), the development program (evolving over time, open-label), and the regulatory program under which this was submitted (fast track, utilizing a rolling review[16]), the application was very challenging to review.

This BLA was submitted over time in "chunks", as additional data cuts were conducted of ongoing data. Unfortunately, some of the data from earlier data cuts were not available for later data cuts, and finding earlier data was challenging, since it could have been included in various documents from a variety of submission dates. In addition, earlier data did not reflect later data as the population enrolled changed over time; therefore how representative these data analyses are, is unclear.

Some of the efficacy challenges and limitations, and questions surrounding efficacy that arose from the review, are as follows:

- Although the endpoints were pre-specified, the investigators used considerable flexibility in enrolling potential patients. It was unclear in some cases what metabolic disorder they were in fact treating, and therefore, what endpoints were relevant.

- There was no placebo, and in many forms of lipodystrophy the natural history is not clearly defined (this is a heterogeneous group of diseases). Therefore, how do we assess the treatment effect?

  – For most patients there was not a narrative of the course of disease prior to study enrollment. In some patients where that information is available, the metabolic disease appeared to wax and wane (particularly hypertriglyceridemia).

- What are the characteristics of patients who are not responding? (and how is "responder" defined?) Without comprehensive and systematic compliance data, it is difficult to attribute poor metreleptin response to poor compliance.

- Dietary intake, a critical part of lipodystrophy management, was not reported; therefore, it is unknown what dietary changes patients made once enrolling in the trial.

- Background medications are significant confounders:

  – Medication changes, including increases or additions of relevant concomitant medications, were made in the first year, prior to the endpoint of interest

  – Background medication compliance was inconsistently recorded

  – It was not clear why some patients were not optimally treated for their metabolic disease(s) prior to enrollment

  – Metreleptin compliance likely covaries with dietary and background medication compliance

- It was not clear what was happening between visits in terms of compliance, diet, medications, laboratory data, illnesses, etc.

- There were a number of data issues from that impacted the confidence in the results:

  – missing data

  – alternative / adjusted baseline visits

  – patient data or information in the BLA was different than that presented in key publications

  - protocol deviations (e.g., NIH Patient 90165 was enrolled without meeting inclusion criteria for metabolic abnormalities; NIH Patient 90146 was enrolled with a baseline leptin concentration that exceeded 12 ng/mL; some patients were started on new medications or had medication doses increased early in the trial)

  - there were several key protocol changes over time

  - secondary efficacy endpoint data from the NIH were not available after the first data cut

  - some patients with elevated hemoglobin (Hb) A1c were not reported as having diabetes mellitus at baseline (therefore calling into question medical history data)

- Some patients were related (e.g., sisters, cousins)[17] and this information was not reported; this could impact the generalizability of the findings

- No formal dose evaluation was conducted

Safety assessment challenges and limitations included:

- Problems in adverse event / disposition reporting, e.g.:

  - Some adverse events were not reported for years (e.g., one case of T-cell lymphoma, one case of breast cancer)

  - Certain discontinuations should have been counted as adverse events rather than “other” or “ineligible to continue”

  - Probably impossible to capture all adverse events, particularly in patients who are only coming into the NIH yearly; in some cases the investigators were informed about hospitalizations months or years later

  - Five patients were reported in the database to have discontinued due to non-compliance, although only four were reported in the Clinical Safety Update report; the one patient (90102) not captured may have had an contributing adverse event that was not reported (worsening renal function)

- Problems with documentation, e.g.:

  - Numerous changes were made to the case report forms, in some cases years later (for example, hand written changes were made to severity, seriousness, or relatedness of an adverse event)

  - Data were entered into case report forms electronically well after the visit, in some cases years later

  - No hospitalization records for cases of pancreatitis were provided in cases where the PI determined the event occurred due to a sudden discontinuation of metreleptin

  - Puberty data were not collected on a case report form and errors were found in the summary tables

- Problems with adverse event / disposition coding, e.g.:

  - A suicide attempt was miscoded as suicidal ideation

  - A patient who was thought to have discontinued due to an adverse event (proteinuria) was later determined to have been transferred to another program in another country

3.2 Compliance with Good Clinical Practices

Dr. Phillip Gorden's (PI, NIH trials) and Dr. Elif Oral's (PI, FHA101) clinical sites were inspected. Both sites received NAI's. The CRO was (b) (4), which also received an NAI. See Dr. Kleppinger's (OSI) clinical inspection summary for details.

3.3 Financial Disclosures

For NIH-sponsored trials 991265 and 20010769, NIH has confirmed that their investigators do not have any reportable conflicts of interests.

Financial disclosure information was provided for the sponsor-initiated FHA101 trial in patients with lipodystrophy and the five pramlintide-metreleptin trials in patients with obesity referenced in the Clinical Addendum **(**DFA101, DFA102, DFA102E, DFA104, and DFA106). For clinical investigators identified as having disclosable financial interests, specific details including the size and nature of the financial interest were provided as an attachment to Form FDA 3455.

- In FHA101 (total N=28), no investigators (out of three) and no sub-investigators disclosed financial interests

- In (b) (6) (total N= (b) (6)), one investigator ((b) (6) and two sub-investigators disclosed financial interests

  - A sub-investigator who enrolled (b) (6) patients is a member of the advisory board for the Amylin/Speakers Bureau exceeding $25,000

  - An investigator who enrolled (b) (6) patients owned (b) (4) shares of Amylin stock

  - A sub-investigator who enrolled (b) (6) patients received honoraria exceeding $25,000

- In (b) (6) (total N (b) (6)), two investigators (of (b) (6)) and no sub-investigators disclosed financial interests

  - An investigator who enrolled (b) (6) patients received a speaking honorarium exceeding $25,000

  - An investigator who enrolled (b) (6) patients owned (b) (4) shares of Amylin stock

- In (b) (6) (total N= (b) (6) enrolled, out of (b) (6) patients from (b) (6)), one investigator (out of (b) (6)) and no sub-investigators disclosed financial interests

  - An investigator who enrolled (b) (6) patients owned (b) (4) shares of Amylin stock

- In (b) (6) (total N= (b) (6) enrolled, N= (b) (6) randomized), one investigator (out of (b) (6) and one sub-investigator disclosed financial interests

  - A sub-investigator who enrolled (b) (6) patients received honoraria / research grant exceeding $25,000

  - An investigator who enrolled (b) (6) patients is a member of the advisory board for Amylin exceeding $25,000

- In DFA106 (total N=419 enrolled out of 784 eligible patients), no investigators (out of 36) and no sub-investigators disclosed financial interests

Reviewer comment: In all cases, the impact of the financial disclosures was mitigated by the fact the trials had multiple sites. The conclusions of the trials were based on the overall data, not from any single investigative site.

No financial information was provided for any of the Amgen-sponsored trials. Upon contact from the BLA sponsor and after reviewing their records, Amgen confirmed that financial disclosures for investigators from the Amgen-sponsored obesity program trials were not found. Furthermore, they have noted that prior to 02 Feb 1999, sponsors of clinical trials such as Amgen were under no obligation to collect this additional information per 21 CFR Part 54 for regulation.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no CMC approvability issues; see Dr. Salazar-Fontana's review for details. See Dr. Tami's memorandum for the rationale of the acceptability of the diluent, bacteriostatic water for injection (BWFI). Although it was noted that there is a small increase in non-dissociable aggregates with BWFI, BWFI has been used since 2007 as the sole diluent in the clinical trials. The clinical experience is adequate to support its use. A PMR will be required to assess aggregate formation.

4.2 Clinical Microbiology

There are no microbiology quality approvability issues; see Dr. Fong's review and addendum for details. Metreleptin is not an antimicrobial, therefore clinical microbiology is not applicable.

4.3 Preclinical Pharmacology/Toxicology

There are no nonclinical approvability issues; see Dr. Basso's review for details. Carcinogenicity studies were not required for BLA approvability as lipodystrophy is an orphan population and further, metreleptin is administered as hormone replacement in this patient population. Finally, as Dr. Bourcier points out in his secondary review, the nature and impact of antidrug antibody responses, including neutralizing activity, in the clinical population cannot be reliably predicted by immune responses observed in rats and dogs exposed to metreleptin.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Clinical evaluations of metreleptin on mechanistic endpoints such as free fatty acids and measures of insulin resistance are described in Section 6.1.5. However, these assessments cannot distinguish whether there is an independent effect of metreleptin on insulin signaling, or if it exerts its effect via appetite alone (i.e., decrease in hyperphagia with subsequent decrease in energy intake). Without a placebo-control, understanding the mechanism of action is important in attempting to distinguish how much of the observed effect may be attributed to the drug versus additional benefits of enrolling in a clinical trial and the subsequent impact via dietary compliance (as well as background medication changes).

It is important to note that caloric intake might make a considerable impact on markers of disease. Wolfsdorf, et al. reported in a 1979 abstract on a 23-year-old female with CGL.[18] At baseline, her *ad libitum* caloric intake was reportedly 2500 kcal/d. Baseline triglyceride (TG) value was 1350 mg/dL, glucose was 137 mg/dL, insulin was 60 µU/mL, and she had hepatomegaly. By report, the patient was placed on a 48-hour fast, then her dietary intake was reduced to 1900 kcal/d for 18 days. At the end of the treatment period, her TG was 80 mg/dL, glucose 77 mg/dL, insulin 8.5 µU/mL, and hepatomegaly was reportedly no longer present. The authors stated, "The reported efficacy of various drugs may reflect their anorectic action and should be compared to the effects of caloric reduction alone."

Furthermore, although energy intake and appetite data were not provided in the BLA, it is reported in the literature[19] that the NIH lipodystrophy patients (at least those reported in this particular publication) decreased energy intake by 45% with metreleptin treatment.

In the BLA there is a report of a patient (90101, a 17-year-old female with AGL) who underwent a controlled withdrawal of metreleptin (see description in Section 6.1.4). Despite reported clamping of caloric intake, her metabolic parameters worsened over several days, supporting the concept of an effect of metreleptin independent of the dietary effects. This is consistent with the effects of metreleptin in paired feeding experiments in animal models of lipodystrophy.[20] However, this was a very severely-affected patient who required weekly plasma exchange therapy due to severe medication-resistant hypertriglyceridemia,[21] and in addition is only a single case, which would therefore require further verification.

4.4.2 Pharmacodynamics

Formal pharmacodynamic assessments were not conducted. See Section 6 for efficacy assessments.

4.4.3 Pharmacokinetics

Mean serum fasting leptin concentrations over the intial two years of metreleptin treatment in an earlier data cut of patients from the NIH trials (N = 55) are presented in the table below; note that considerable variability (minimum and maximum) was seen.

Table 5. Fasting Concentrations of Serum Leptin, NIH Trials 2009 Datacut (N = 55)

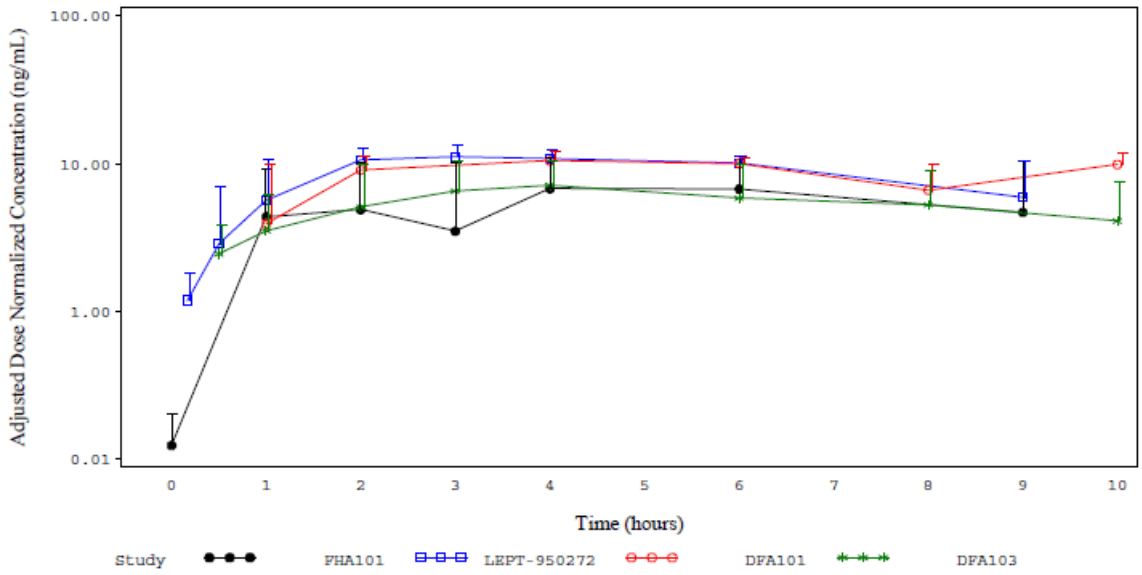
	Baseline		Visit			
	Statistics	Baseline [1]	Month 4	Month 8	Month 12	Year 2
Fasting Leptin (ng/mL)	n	51	34	34	34	19
	Mean (SE) [2]	2.8 (0.39)	18.6 (2.7)	30.0 (4.1)	29.9 (4.7)	24.5 (5.6)
	Min, Max	0.3, 14.1	1.1, 62.2	1.86, 82.6	2.2, 96.9	1.7, 82.1

SAP = statistical analysis plan; SD = standard deviation; SE = standard error.
[1] In general, baseline measurements were defined as the last as the last available value before the subject received the first injection of metreleptin. See SAP for details.
[2] Leptin concentrations at baseline are presented in mean (SE).
Notes: Data are shown for the ITT patients for whom leptin concentrations were available at each time point. The time of last metreleptin dose prior to fasting leptin blood sample was not collected.

Source: Summary of Clinical Pharmacology, Table 5

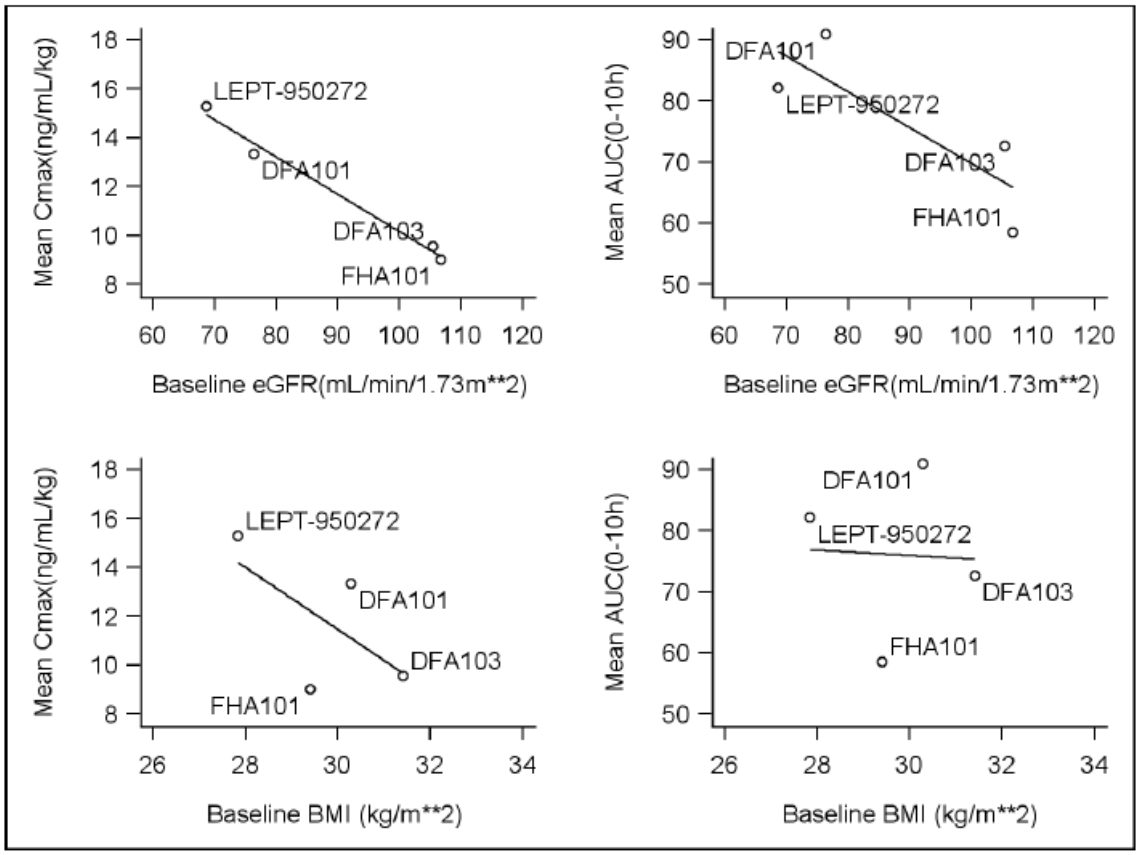
The pharmacokinetic (PK) properties of metreleptin in lipodystrophy patients were assessed in a subset of patients with lipodystrophy from the FHA101 trial [conducted by the sponsor under a treatment IND, see Section 5.3 and Section 9.4 (Appendix)]. The limited number of lipodystrophy patients with PK profiles available for the analyses should be considered when interpreting these results. The PK properties of metreleptin for the subset of patients from FHA101 were then compared to the PK properties of metreleptin in healthy normal weight individuals and overweight and obese patients from the Amgen trial LEPT-950272, and Amylin trials DFA101 and DFA103. The PK properties of metreleptin (C_{max}, $AUC_{0\text{-}10h}$ and T_{max}) were similar between the lipodystrophy patients and healthy individuals after correcting for differences in renal function (with higher estimated GFR in lipodystrophy patients compared to healthy individuals).

Figure 2. Mean (+SD) Metreleptin Pharmacokinetic Profiles (Baseline Adjusted and Dose Normalized) after a Single Dose of Metreleptin, FHA101, LEPT-950272, DFA101, and DFA103 Trials



Source: Technical Report REST120204, Figure 2

Figure 3. Mean Metreleptin Exposure (C_{max} and AUC_{0-10h}) versus Mean eGFR or Baseline BMI, FHA101, LEPT-950272, DFA101, and DFA103 Trials

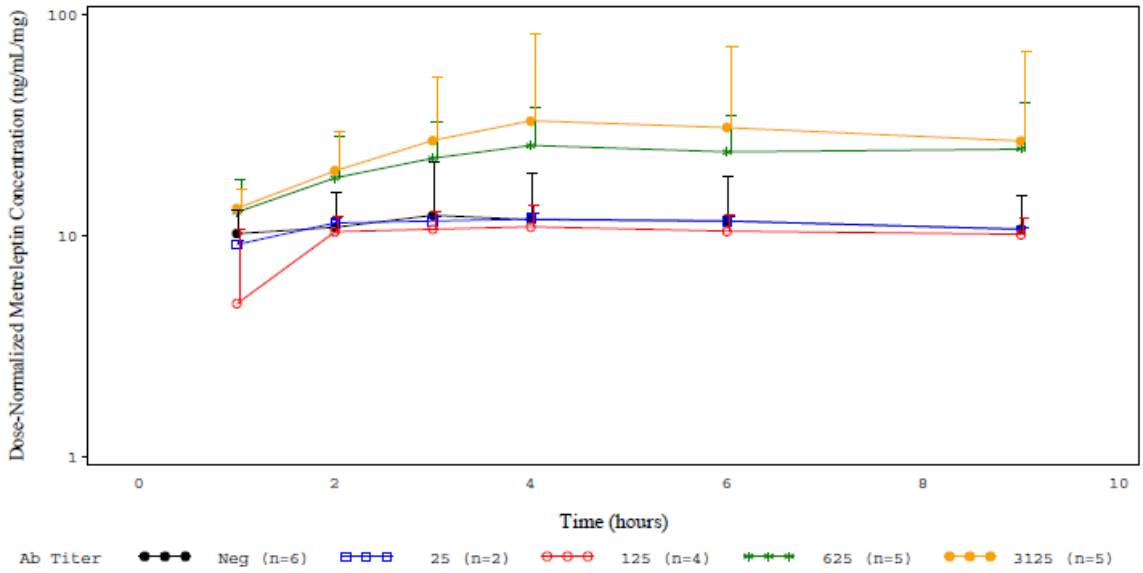


Source: Technical Report REST120204, Figure 3

Exploratory plots of metreleptin exposure over time for FHA101 suggest that higher exposure of metreleptin occurs with higher antibody titers (e.g., 625 and 3125). The effect of antibody titers greater than 3125 could not be assessed due to negative interference in the immunoassay of leptin (including metreleptin) concentrations. Higher plasma exposure of metreleptin with higher antibody titers in lipodystrophy patients is consistent with the observations made in studies of otherwise healthy overweight/obese people.**

** As reported by the sponsor.

Figure 4. Mean Concentration-Time Profiles of Metreleptin (PK1 and PK2 Combined) Stratified by Antibody Titer (Dose Normalized)



Source: Technical Report REST120204, Figure 5

For FHA101, metreleptin was initially administered as a twice a day (BID) dosing regimen with the option to change from BID to once a day (QD) dosing using the same total daily dose once metabolic parameters had stabilized. The daily exposures of metreleptin for the QD dosing regimen were consistent with the BID dosing regimen when the same total daily dose was administered.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6. Studies Supporting the Metreleptin for Lipodystrophy BLA

Study	Patient Population	Number of Metreleptin-Treated Patients	Position in BLA	Endpoints Supported
NIH Trials 991265/20010769 [1]	Lipodystrophy patients	72 [2]	Pivotal	Safety and efficacy
Treatment IND FHA101 [1]	Lipodystrophy patients	28 [3]	Supporting	Safety and efficacy
Amgen 5-trial ISS (metreleptin monotherapy)	Obese patients without lipodystrophy	784 (vs. 351 placebo)	Supporting	Safety (including immunogenicity)
Other 10 Amgen obesity trials (metreleptin monotherapy)	Obese patients without lipodystrophy	379 [4] (vs. 167 placebo)	Supporting	Immunogenicity
Amylin obesity program (metreleptin/pramlintide combination)	Obese patients without lipodystrophy	615 (vs. 203 placebo)	Supporting	Immunogenicity

NASH=non-alcoholic steatohepatitis; HA=hypothalamic amenorrhea; DM=diabetes mellitus
[1] ongoing trials or ongoing treatment, except investigator-initiated study with C. Levy Marchal as principal investigator
[2] As of 11 July 2011 data cut
[3] As of 7 Mar 2012 data cut
[4] Excludes 4 patients with congenital leptin deficiency treated with metreleptin in Amgen trial 970161

Source: BLA 125390, Section 2.5 Clinical Overview, date 27 Mar 2013; sponsor response to FDA 24 Jun 2013, Table 3

5.2 Review Strategy

I was the primary reviewer for clinical efficacy and safety. I received input from the FDA statistics reviewer and clinical reviewers from the Divisions of Hematology Products, Pulmonary, Allergy, and Rheumatology Products, and Gastrointestinal and Inborn Errors Products.

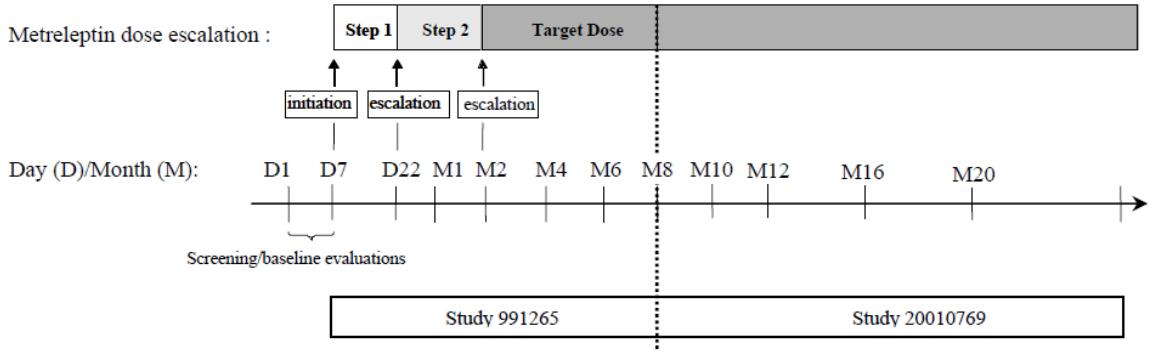
5.3 Discussion of Individual Studies/Clinical Trials

NIH Trials

Trial 991265-20010769 is entitled, *a long-term, open-label study to evaluate the effect of leptin replacement on efficacy and safety in patients with lipodystrophy*. The original protocol (991265) was submitted under IND 60534 in June 2000, with two subsequent protocol amendments. The trial was conducted at the Clinical Centers of the National

Institutes of Health (NIH) and the University of Texas Southwestern in Dallas (UTSW).[††] At that time, metreleptin drug substance was manufactured by Amgen. The eligibility requirements, the program of metreleptin administration, and major endpoints comprised the core protocol that both centers followed. Each center also conducted individual assessments of additional parameters based on their specific research interest and available facilities. The basic visit structure of protocol 991265 is illustrated in the following schematic:

Figure 5. Study Overview and Visit Structure for Patients Enrolled in Study 991265



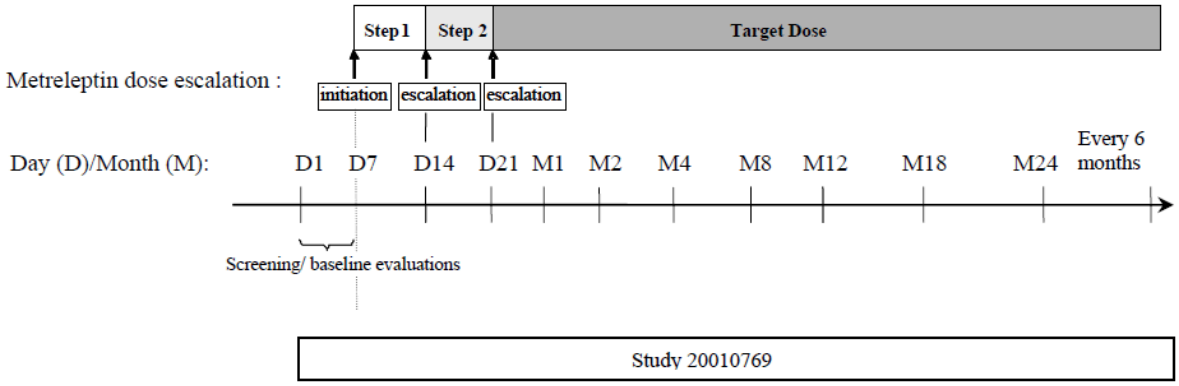
[1] Metreleptin target dose was achieved via a 2-step dose escalation per protocol.
[2] Following the first metreleptin dose on Day 7, patients were observed as inpatients for at least 48 hours. Patients were not required to visit the site on Day 22

Source: Clinical Efficacy Update, Appendix 1

The long-term protocol (20010769) was designed to continue and expand protocol 991265 by (1) lowering the inclusion age criterion from 14 years and older to 5 years and older, (2) evaluating long-term (one-year) efficacy, and (3) including patients with less severe leptin deficiency. The basic visit structure for protocol 20010769 is illustrated in the following schematic:

[††] Note that only the data from the NIH is included in the BLA submission, due to previous agreements with the Agency. Patients 1 and 2 from the UTSW site continued metreleptin treatment under 991265 until January 2003, after which they enrolled in an investigator study under a separate research IND and continued metreleptin treatment. Patient 1 is still on metreleptin treatment, while Patient 2 withdrew in January 2008 due to inconvenience of participation in the study including travel to study site. The third patient at UTSW continued metreleptin treatment under 991265 until June 2002 after which he was lost to follow up, although the investigator indicated that the patient was “alive and well” several years after discontinuation of metreleptin.

Figure 6. Study Overview and Visit Structure for Patients Enrolled in Study 20010769



[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.

Source: Clinical Efficacy Update, Appendix 1

Subsequently five amendments were made to the protocol; key changes included increasing sample size, expanding entry criteria to include patients with progressively less severe leptin-deficiency, lowering age of entry to 6 months, and changing the dosing regimen.[‡‡]

Summaries of Protocols 991265 and 20010769 can be found in Section 9.4 (Appendix) of this review.

[‡‡] Regarding dosing changes, the following comment was noted in Protocol 20010769: *A new Appendix 7 was added to the protocol document (pages 52-53) to layout current proposed dosing in chart form. These proposed doses are based on the observations of 38 patients that we have treated on leptin therapy for 3 months up to 6 years. Doses have needed to be increased from earlier versions, as target levels for glycemia and lipids levels are trying to be achieved. For example in 6 women with partial lipodystrophy, only 2 were able to achieve target levels for glycemia after 1 year, and 1 patient for both glycemia and lipids. But when the dose of leptin was increased to 0.12 mg/kg/day along with maximizing their existing standard therapies, all had HbA1c levels less than 8.0% and 5 out of 6 had HbA1c levels less than 7%. This new chart will assist in dose escalations, and double checking by the pharmacy of leptin therapy ordered.* ***Reviewer comment: It is noted in these patients with partial lipodystrophy that efficacy was achieved when, in addition to increasing the leptin dose, existing standard therapies were maximized. Efficacy of metreleptin is very difficult to assess in such situations where multiple interventions were performed simultaneously. This issue was explored further in Section 6.***

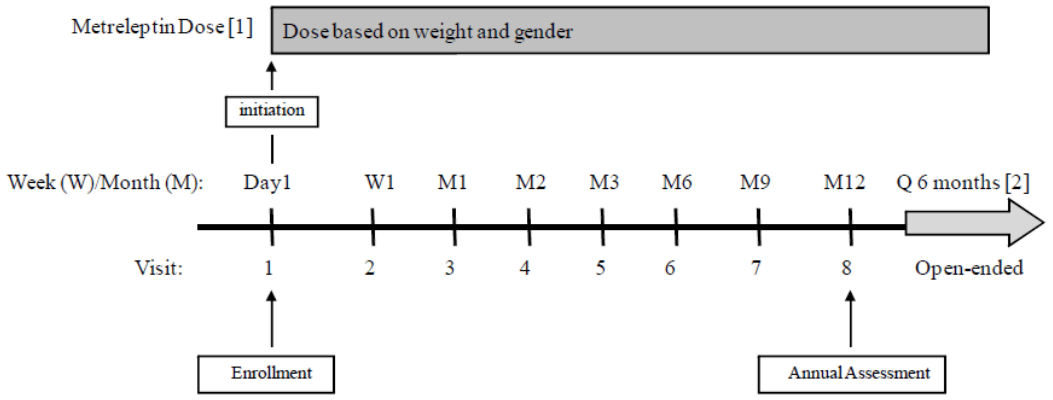
FHA101 Trial

The FHA101 trial was initiated under a treatment IND in 2008 in order to provide expanded access to lipodystrophy patients while the sponsor prepared the data needed for the BLA submission.

FHA101 differed from the NIH trials in several respects; therefore, data from FHA101 were considered by the sponsor to be supplemental in nature: (1) the majority of patients enrolled in FHA101 were patients with partial lipodystrophy, (2) eligibility criteria did not include leptin concentrations, (3) compared to patients in the NIH protocol (initiated in 2000), patients in FHA101 had a shorter exposure to metreleptin, and (4) the data collected for FHA101 were more limited in scope than for the NIH trials, focusing on key efficacy and safety parameters that are typically collected as part of routine clinical care of patients with diabetes mellitus and/or hypertriglyceridemia.

The protocol for FHA101 is summarized in Section 9.4, and the basic study design including the approach to metreleptin dosing is illustrated in the following schematic:

Figure 7. FHA101 Study Design



[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.

Source: Clinical Efficacy Update, Appendix 2

The protocol has three amendments:

- Amendment 1 included:
    - additional assessments (vital signs and documentation of Tanner stage for pediatric patients)
    - clarification of the minimum age of patients who can enroll
    - instruction regarding height measurement for pediatric patients
- Amendment 2:
    - removed some of the routine laboratory assessments that were not considered necessary from a standard of care perspective and clarified some of the procedures required at standard, maintenance, and unscheduled visits
    - updated the efficacy and safety endpoints [added CBC, vital signs, and Tanner staging], analysis methods, justification of sample size, and blood volume sections
- Amendment 3:
    - simplified the treatment protocol for physicians intending to treat patients with diabetes mellitus and/or hypertriglyceridemia associated with lipodystrophy with metreleptin
    - An addendum to amendment 3 was also added that nearly replicated amendment 2 (prior "research" version). One investigator (Dr. Elif Oral, University of Michigan site) initiated metreleptin treatment for lipodystrophy patients on metreleptin treatment under amendment 2. Sites who have both the resources and interest in carrying out a more research-oriented version of the protocol with specified efficacy and safety assessments could conduct metreleptin treatment under the addendum. To date, Dr. Oral's site is the only one with patients enrolled under the addendum.

Therefore, to clarify, amendment 3 is the simplified treatment protocol and the addendum to amendment 3 is the research-oriented treatment protocol.

6 Review of Efficacy

Efficacy Summary

Without a placebo group or adequate historical control, it is challenging to attribute beneficial changes to metreleptin versus improvements in diet or enhanced compliance with concomitant antihyperglycemic or lipid-lowering medications. Furthermore, a substantial amount of missing data, variable duration of therapy, variation in the timing of efficacy assessments, variable and within-trial adjustment of background therapies, compliance that was not systematically documented, and protocol changes add to the challenges of isolating the effect of metreleptin on metabolic control in this application. Nevertheless, a subgroup of patients appears to have achieved benefits from metreleptin that would be unlikely to have been achieved spontaneously: patients with generalized lipodystrophy (congenital or acquired) with severe insulin resistance resulting in diabetes mellitus and / or severe hypertriglyceridemia not adequately controlled with other therapies. The apparent response of this subgroup overall is consistent with that of the small group of patients from the initial trial 991265, and further, is consistent with the mechanism of action of leptin. Metreleptin appears to treat the insulin resistance of lipodystrophy; to the extent diabetes and hypertriglyceridemia are the result of insulin resistance, metreleptin treatment is associated with improvements in, and in some cases normalization of, metabolic control. The table below highlights the differences at 12 months in the key efficacy endpoints of hemoglobin (Hb) A1c, fasting plasma glucose (FPG), and triglycerides (TG) between the patients with generalized lipodystrophy and patients with partial lipodystrophy. In addition, the improvements are accentuated in those patients with uncontrolled diabetes mellitus (defined here as HbA1c 7% or greater or FPG 126 mg/dL or greater) or severe hypertriglyceridemia (defined here as TG 500 mg/dL or greater), supporting the drug's efficacy in treating these diseases.

Table 7. Key Efficacy Parameters at Baseline and Month 12 in Generalized and Partial Lipodystrophy: All Patients and Patients with Elevated HbA1c, FPG, and TG; NIH Trials

HbA1c, %	All			Baseline HbA1c ≥ 7%		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	29	8.7 (0.4)	-2.0 (0.3)	24	9.3 (0.3)	-2.4 (0.5)
Partial	21	7.5 (0.5)	-0.4 (0.2)	11	9.2 (0.5)	-1.0 (0.4)
Fasting glucose, mg/dL	All			Baseline FPG ≥ 126 mg/dL		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	31	179.5 (15.9)	-48.3 (16.9)	21	218.6 (17.8)	-82.1 (16.5)
Partial	21	155.8 (19.3)	-32.1 (14.8)	11	220 9 (22.5)	-68.6 (23.2)
TG, mg/dL	All			Baseline TG ≥ 500 mg/dL		
	n	Baseline Median	Δ from baseline at Month 12 Median	n	Baseline Median	Δ from baseline at Month 12 Median
Generalized	30	414.5	-246.5	12	1526.5	-1117.0
Partial	21	357.0	-74.0	7	1237.0	-499.0

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 3

The severity of metabolic abnormalities at baseline was more heterogenous in patients with partial lipodystrophy in the NIH trials and, overall, the observed reductions in HbA1c and TG were less than those observed in patients with generalized lipodystrophy. Furthermore, whereas the majority of patients in the NIH trials with generalized lipodystrophy on concomitant anti-hyperglycemic medications at baseline discontinued or had significant reduction in the doses of anti-hyperglycemics at Month 12, a greater proportion of patients with partial lipodystrophy versus generalized lipodystrophy had anti-hyperglycemic medications added to their regimen or doses increased, including two patients with partial lipodystrophy who added insulin to their regimen by Month 12. Similarly, although the majority of patients on lipid-lowering medications at baseline had regimens unchanged at Month 12, the two patients who discontinued all lipid-lowering medication at Month 12 had generalized lipodystrophy, whereas the six patients whose dose of fibrate was increased or who had a lipid-lowering drug added (fibrate or non-fibrate) at Month 12 had partial lipodystrophy.

Because of the smaller reductions in metabolic parameters and confounding by concomitant medications in patients with partial lipodystrophy, it is unclear if a subgroup of patients with partial lipodystrophy can be clearly identified who may benefit from metreleptin. Baseline fasting leptin could be an important factor, particularly given the observation that lipodystrophy patients in earlier versions of the NIH protocol were selected on the basis of low fasting leptin values (originally defined as less than 4 ng/mL in females and less than 3 ng/mL in males) and appeared to have a more pronounced changes in metabolic parameters during metreleptin treatment.

Over the entire NIH cohort, patients with generalized lipodystrophy had mean (SD) fasting leptin of 1.3 (1.1) ng/mL and those with partial lipodystrophy had a value of 4.9 (3.1) ng/mL. The relationship between baseline leptin and changes in metabolic parameters associated with metreleptin treatment was specifically evaluated in patients with partial lipodystrophy who had a wider range of baseline leptin values compared with patients with generalized lipodystrophy who almost all had “low” leptin levels. Across all three endpoints (i.e., HbA1c, FPG, and TG), a greater change from baseline was observed for patients with low baseline leptin concentration in patients with partial lipodystrophy (Table 8). For example, while the average change from baseline in HbA1c at Month 12 was -0.9% for patients with partial lipodystrophy and low leptin levels, it was only -0.1% for patients with partial lipodystrophy and higher leptin levels.

Table 8. Change From Baseline to Month 12 in Key Efficacy Parameters by Leptin Categories; NIH Trials

	Mean (SE) HbA1c (%)			Mean (SE) FPG (mg/dL)			Median TG (mg/dL)		
	N	Baseline	Δ from BL at Mo 12	N	Baseline	Δ from BL at Mo 12	N	Baseline	Δ from BL at Mo 12
Generalized									
All									
Low leptin	26	8.6 (0.4)	-2.1 (0.3)	28	176 (17)	-48 (18)	28	415	-247
Higher leptin	1	10.1 (na)	-1.6 (na)	1	200 (na)	-134 (na)	1	158	-105
Elevated Baseline	Baseline HbA1c ≥ 6%			Baseline FPG ≥ 126 mg/dL			Baseline TG ≥ 200 mg/dL		
Low leptin	23	9.1 (0.4)	-2.4 (0.3)	18	219 (20)	-87 (18)	20	562	-395
Higher leptin	1	10.1 (na)	-1.6 (na)	1	200 (na)	-134 (na)	-	-	-
Partial									
All									
Low leptin	10	7.6 (0.9)	-0.9 (0.4)	10	178 (33)	-56 (27)	10	609	-237
Higher leptin	11	7.5 (0.5)	-0.1 (0.2)	11	136 (22)	-11 (13)	11	343	-64
Elevated Baseline	Baseline HbA1c ≥ 6%			Baseline FPG ≥ 126 mg/dL			Baseline TG ≥ 200 mg/dL		
Low leptin	6	9.2 (1.0)	-1.6 (0.4)	6	239 (36)	-99 (34)	8	1020	-429
Higher leptin	8	8.1 (0.5)	-0.2 (0.2)	5	199 (26)	-32 (24)	8	358	-65

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 5

In summary, replacement or supplementation of leptin with metreleptin is associated with improvements in the metabolic complications of lipodystrophy, although importantly, it does not treat the underlying disorder. Patients with generalized forms of lipodystrophy and significant insulin resistance appear to achieve the best results, including large and in some cases sustained improvements in HbA1c and TG, often accompanied by a discontinuation or decrease of anti-hyperglycemic or lipid-lowering therapies.

By contrast, patients with partial forms of lipodystrophy have a more varied, attenuated, and confounded response. There may be a subset of patients with partial lipodystrophy with very low leptin concentrations and significant metabolic disease that responds to metreleptin, although confounders and missing data present challenges that may be very difficult to overcome in a trial that lacks a comparator.

6.1 Indication

Treatment of metabolic disorders associated with lipodystrophy (see proposed language in Section 2.1, Product Information).

6.1.1 Methods

The statistical analysis plan provided for the NIH trials was written by the sponsor in 2010; therefore, all efficacy analyses are considered to be post-hoc.

The pivotal efficacy data are based on 72 patients with lipodystrophy treated with metreleptin in two open-label, investigator-sponsored trials conducted at the NIH: Study

991265 (completed) and Study 20010769 (ongoing). These 72 patients constitute the Intent-to-Treat (ITT) population, defined as having received at least one dose of metreleptin. Supporting efficacy data are based on 28 patients with lipodystrophy treated with metreleptin under a treatment IND at three sites (with 25 patients enrolled at the University of Michigan site) as of a data cutoff of 07 Mar 2012.

The efficacy review focuses on the trials conducted in the lipodystrophy population: NIH 991265/20010769 (hereafter referred to as the NIH trials, unless one of the two NIH trials is specifically being discussed), and FHA101.

Although additional evaluation of metreleptin efficacy was conducted by the sponsor and various researchers for a variety of conditions, including multi-factorial obesity, obesity associated with congenital leptin deficiency, severe insulin resistance, and others (see Table 41 in Section 7.1.1), the efficacy of metreleptin in these conditions may not be relevant to the proposed indication under this BLA, and therefore, will not be extensively addressed. Available safety findings from these investigational programs are reviewed under Section 7.

6.1.2 Demographics

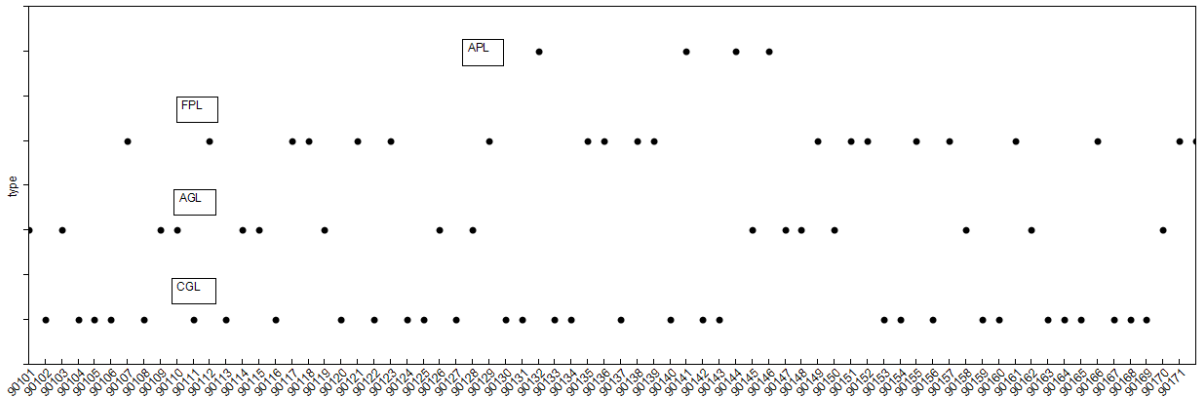
NIH Trials

The overall population was predominantly female (83%) and white (61%). There were no male patients enrolled with partial lipodystrophy. More patients had generalized than partial lipodystrophy, and congenital / familial lipodystrophy was more prevalent than acquired types. Patients diagnosed with generalized lipodystrophy were, on average, younger than those diagnosed with partial lipodystrophy. Similar numbers of pediatric (less than 18 years of age) and adult (18 years of age or older) patients were enrolled.

The following figure illustrates the enrollment of the NIH patients by lipodystrophy type.[§§] Note that patients were enrolled in order of patient number. Over time, more patients with partial lipodystrophy were enrolled. This is likely a reflection of the progressive loosening of leptin concentration inclusion criteria over the course of the ongoing enrollment.

[§§] Reviewer comment: Of note, two of the patients with FPL are sisters (90112 and 90117) and one (90123) is their cousin. This information was not reported in the clinical efficacy documents in the BLA, but was reported in Park, et al (reference 17).

Figure 8. NIH Enrollment



Source: Reviewer generated from BLA 125390 datasets

Metabolic abnormalities tended to be more severe in female patients, as compared to males. Among females, HbA1c elevation was more severe in patients with generalized lipodystrophy than than those with partial lipodystrophy. Female patients with partial lipodystrophy had higher baseline mean TG than those with generalized lipodystrophy (male or female), while female patients with generalized lipodystrophy had the highest proportion of patients with TG 1000 mg/dL or greater.

The following table enumerates demographics and baseline characteristics of patients in the trials by generalized lipodystrophy, partial lipodystrophy, and overall. The table that follows provides an enumeration of medical history by lipodystrophy subtype.

Table 9. Demographics and Baseline Characteristics by Generalized and Partial Lipodystrophy, NIH Trials

	Generalized N=48	**Partial N=24**	**Total N=72**
Sex, n (%)			
Male	12 (25.0)	0	12 (16.7)
Female	36 (75.0)	24 (100)	60 (83.3)
Race, n (%)			
White	22 (45.8)	22 (91.7)	44 (61.1)
Black	9 (18.8)	0	9 (12.5)
Asian	2 (4.2)	1 (4.2)	3 (4.2)
Native American	2 (4.2)	0	2 (2.8)
Hispanic	10 (20.8)	0	10 (13.9)
Other	3 (6.3)	1 (4.2)	5 (5.6)
Age (years)			
Mean (SD)	18.7 (14.0)	33.7 (16.0)	23.7 (16.2)
Min, Max	1, 68	2, 64	1, 68
Age Group, n (%)			

≤ 12	14 (29.2)	3 (12.5)	17 (23.6)
> 12 - < 18	21 (43.8)	1 (4.2)	22 (30.6)
≥ 18 - ≤ 65	12 (25.0)	20 (83.3)	32 (44.4)
> 65	1 (2.1)	0	1 (1.4)
< 18	35 (73.0)	4 (16.7)	39 (54.2)
≥ 18	13 (27.1)	20 (83.3)	33 (45.8)
Lipodystrophy Type			
Congenital/Familial	32 (66.7)	20 (83.3)	52 (72.2)
Acquired	16 (33.3)	4 (16.7)	20 (27.8)
Fasting Leptin (ng/mL) †			
Mean (SD)	1.3 (1.1)	4.9 (3.1)	2.6 (2.6)
Min, Max	0.3, 5.2	1.0, 14.1	0.3, 14.1
Leptin Categories, n (%)			
Lower (M < 2, F < 4)	42 (87.5)	11 (45.8)	53 (73.6)
Higher (M ≥ 2, F ≥ 4)	2 (4.2)	13 (54.2)	15 (20.8)
HbA1c (%)			
Mean (SD)	8.5 (2.1)	7.7 (2.2)	8.2 (2.2)
Min, Max	4.5, 13.7	4.6, 13.3	4.5, 13.7
HbA1c Categories, n (%)			
< 6	8 (16.7)	7 (29.2)	15 (20.8)
≥ 6 to < 7	2 (4.2)	4 (16.7)	6 (8.3)
≥ 7 to < 9	18 (37.5)	6 (25.0)	24 (33.3)
≥ 9	19 (39.6)	7 (29.2)	26 (36.1)
Fasting Plasma Glucose (FPG)			
Mean (SD)	183.9 (86.8)	162.3 (93.0)	176.7 (88.8)
Min, Max	71, 478	49, 367	49, 478
FPG Categories, n (%)			
< 100	7 (14.6)	8 (33.3)	15 (20.8)
≥ 100 to < 126	8 (16.7)	3 (12.5)	11 (15.3)
≥ 126	33 (68.8)	13 (54.2)	46 (63.9)
Fasting TG (mg/dL)			
Mean (SD)	858.7 (1312.8)	1398.8 (3091.5)	1041.3 (2083.1)
Median	368.0	358.0	359.0
Min, Max	49, 7420	101, 12697	49, 12697
Fasting TG Categories, n (%)			
< 200	12 (25.0)	5 (20.8)	17 (23.6)
≥ 200 to < 350	10 (20.8)	6 (25.0)	16 (22.2)
≥ 350 to < 500	8 (16.7)	6 (20.8)	13 (18.1)
≥ 500 to < 1000	6 (12.5)	3 (12.5)	9 (12.5)
≥ 1000	11 (22.9)	5 (20.8)	16 (22.2)
HbA1c and TG Categories, n (%)			
A1c < 6 AND TG < 200	5 (10.4)	2 (8.3)	7 (9.7)
A1c < 6 AND TG ≥ 200	3 (6.3)	5 (20.8)	8 (11.1)
A1c ≥ 6 AND TG < 200	7 (14.6)	3 (12.5)	10 (13.9)
A1c ≥ 6 AND TG ≥ 200	31 (64.6)	14 (58.3)	45 (62.5)

A1c ≥ 6 OR TG ≥ 200	43 (89.6)	22 (91.7)	65 (90.3)
A1c ≥ 7 OR TG ≥ 350	41 (85.4)	20 (83.3)	61 (84.7)
ALT (U/L)			
Mean (SD)	115.0 (123.0)	58.2 (59.7)	96.1 (109.4)
Min, Max	18, 726	16, 232	16, 726
ALT Categories, n (%)			
< 41	12 (25.0)	14 (58.3)	26 (36.1)
≥ 41	36 (75.0)	10 (41.7)	46 (63.9)
AST (U/L)			
Mean (SD)	81.5 (78.6)	40.6 (37.1)	67.9 (70.1)
Min, Max	15, 380	9, 153	9, 380
AST Categories, n (%)			
< 34	16 (33.3)	16 (66.7)	32 (44.4)
≥ 34	32 (66.7)	8 (33.3)	40 (55.6)

* Lower limit of quantitation (LLOQ) for leptin concentration is 0.3 ng/mL; values < LLOQ are reported as 0.3 ng/mL
† The entry criteria for leptin evolved over time. Initially < 4.0 ng/mL [females] or < 3.0 ng/mL [males]) and in 2008 amended to < 12.0 ng/mL in females ≥ 5 yrs and < 8.0 ng/mL in males ≥ 5 yrs, and < 6 ng/mL in 6 mos to < 5 yrs.

Source: Clinical Efficacy Update, Table 6

Table 10. Relevant Medical History by Lipodystrophy Subtype

Medical Term	AGL (N = 16) n (%)	CGL (N = 32) n (%)	APL (N = 4) n (%)	FPL (N = 20) n (%)	All Subjects (N = 72) n (%)
DIABETES MELLITUS	11 (68.8)	25 (78.1)	3 (75.0)	19 (95.0)	58 (80.6)
HYPERTRIGLYCERIDEMIA	8 (50.0)	19 (59.4)	3 (75.0)	17 (85.0)	47 (65.3)
ACANTHOSIS NIGRICANS	7 (43.8)	25 (78.1)	4 (100.0)	4 (20.0)	40 (55.6)
STEATOHEPATITIS	10 (62.5)	10 (31.3)	4 (100.0)	8 (40.0)	32 (44.4)
HEPATOMEGALY	7 (43.8)	17 (53.1)	1 (25.0)	5 (25.0)	30 (41.7)
HYPERTENSION	2 (12.5)	14 (43.8)	1 (25.0)	11 (55.0)	28 (38.9)
PROTEINURIA	8 (50.0)	13 (40.6)	1 (25.0)	2 (10.0)	24 (33.3)
HYPERLIPIDEMIA	4 (25.0)	8 (25.0)	1 (25.0)	5 (25.0)	18 (25.0)
PANCREATITIS	4 (25.0)	4 (12.5)	1 (25.0)	7 (35.0)	16 (22.2)
INSULIN RESISTANCE	1 (6.3)	7 (21.9)	2 (50.0)	5 (25.0)	15 (20.8)
HEPATIC STEATOSIS	2 (12.5)	6 (18.8)	0 (0.0)	6 (30.0)	14 (19.4)
DEPRESSION	3 (18.8)	5 (15.6)	0 (0.0)	4 (20.0)	12 (16.7)
POLYCYSTIC OVARY SYNDROME	1 (6.3)	4 (12.5)	1 (25.0)	6 (30.0)	12 (16.7)
AMENORRHEA	3 (18.8)	5 (15.6)	0 (0.0)	3 (15.0)	11 (15.3)
HEADACHES	2 (12.5)	7 (21.9)	1 (25.0)	1 (5.0)	11 (15.3)
HIRSUTISM	0 (0.0)	6 (18.8)	1 (25.0)	4 (20.0)	11 (15.3)
HEPATOSPLENOMEGALY	3 (18.8)	5 (15.6)	0 (0.0)	0 (0.0)	8 (11.1)
XANTHOMAS	2 (12.5)	2 (6.3)	0 (0.0)	4 (20.0)	8 (11.1)
ANEMIA	2 (12.5)	2 (6.3)	0 (0.0)	3 (15.0)	7 (9.7)
HYPERCHOLESTEROLEMIA	1 (6.3)	5 (15.6)	0 (0.0)	1 (5.0)	7 (9.7)
VITAMIN D DEFICIENCY	2 (12.5)	4 (12.5)	0 (0.0)	1 (5.0)	7 (9.7)
ASTHMA	3 (18.8)	2 (6.3)	0 (0.0)	1 (5.0)	6 (8.3)
CIRRHOSIS	1 (6.3)	5 (15.6)	0 (0.0)	0 (0.0)	6 (8.3)
FATIGUE	3 (18.8)	1 (3.1)	0 (0.0)	2 (10.0)	6 (8.3)
NEUROPATHY	2 (12.5)	2 (6.3)	1 (25.0)	1 (5.0)	6 (8.3)
DIABETIC RETINOPATHY	0 (0.0)	1 (3.1)	0 (0.0)	4 (20.0)	5 (6.9)
OVARIAN CYSTS	1 (6.3)	2 (6.3)	0 (0.0)	2 (10.0)	5 (6.9)

Note: - Relevant medical history terms were identified by a sponsor review.

Source: Clinical Efficacy Update, Supporting Data Summary 1.4

Seven patients were enrolled with baseline HbA1c less than 6% and TG less than 200 mg/dL (see Table 11 below). [Recall that patients in the NIH trials had to have either: diabetes mellitus (1997 criteria), fasting insulin greater than 30 µU/mL, or fasting TG greater than 200 mg/dL, therefore, presumably patients in this group would have been

enrolled based on insulin resistance.] Six of the seven patients with baseline HbA1c less than 6% and TG less than 200 mg/dL were pediatric (age less than 18 years), five of whom were less than 12 years old. The one adult patient (90157) with normal HbA1c and TG at baseline had a history of diabetes and hypertriglyceridemia but good metabolic control at the baseline assessment. All seven patients had elevated baseline ALT (41 U/L or greater) and/or AST (34 U/L or greater) or had a history of hepatomegaly, hepatic steatosis, and/or steatohepatitis.[***] Patient 90165 (2-year-old female with CGL, see bolded row in the table below) had only a mildly elevated AST and a history of hepatic steatosis without diabetes, hypertriglyceridemia, or insulin resistance.[†††]

Table 11. Baseline Characteristics of Patients Enrolled with HbA1c Less than 6% and TG Less than 200 mg/dL

Patient	Age	Sex	Subtype	Insulin (µU/mL)	ALT (U/L)	AST (U/L)	FPG (mg/dL)	HbA1c (%)	TG (mg/dL)	Leptin (ng/mL)
90131	9	M	CGL	43.9	177	85	79	4.5	137	0.5
90134	9	M	CGL	110	386	258	71	5.5	122	0.5
90144	10	F	APL	57.6	90	48	80	4.6	108	1.12
90150	11	M	AGL	89.6	726	380	105	5	141	0.46
90157	30	F	FPL	25.7	68	35	83	5.3	101	4.61
90160	14	F	CGL	79	55	28	95	5.6	117	NA
90165	**2**	**F**	**CGL**	**6.6**	**28**	**37**	**90**	**4.9**	**193**	**2.41**

Source: Reviewer derived from BLA datasets (Clinical Safety Update, DLABS 2)

Additional examples of patients with outlier laboratory values at baseline include: (1) a qualifying leptin concentration for one patient (90146, 27-year-old female with APL) that exceeded 12 ng/mL; the investigator allowed the patient to enroll based on an earlier value reported to be 12 ng/mL,[‡‡‡] and (2) one patient (90150, 11-year-old male with AGL) had very high liver enzymes at baseline (ALT 726 U/L and AST 380 U/L).

[***] It was stated that the investigator generally enrolled patients with insulin resistance only if they also presented with clinically significant liver disease - reported as hepatic steatosis and/or steatohepatitis - although it is unknown if these patients received liver biopsy in order to make these diagnoses.

[†††] Although the sponsor states that the inclusion of Patient 90165 was consistent with the protocol inclusion criteria for patients age 5 years or younger, I could not find that the requirement for metabolic abnormalities (diabetes, fasting insulin > 30 µU/mL, or hypertriglyceridemia) was changed when patients younger than 5 years of age were allowed to enter the trial in a later protocol amendment (in fact, the triglyceride criteria was changed to accommodate the fact that fasting TG would not be able to be obtained in infants). Therefore, her inclusion in the trial with no history of diabetes mellitus and baseline laboratory values of FPG 90 mg/dL, HbA1c 4.9%, TG 193 mg/dL, and insulin 6.6 µU/mL, appears to have been a protocol violation.

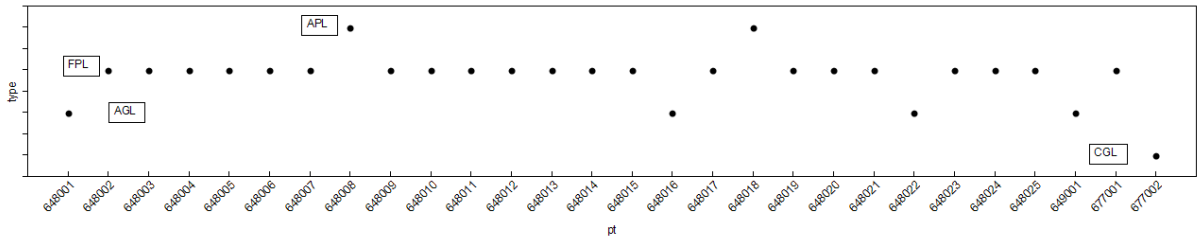
[‡‡‡] Nevertheless, this is a protocol violation.

FHA101 Trial

Of the 28 patients enrolled in the trial by the 7 Mar 2012 datacut, the population was predominantly female (92.9%) and white (75.0%). Five (18%) were diagnosed with generalized lipodystrophy (one congenital and four acquired), and 23 (82%) patients were diagnosed with partial lipodystrophy (21 familial and two acquired). The two male patients enrolled in the trial were diagnosed with AGL and FPL, respectively. Of 28 patients, 25 (89%) were 18 years or older. Patients diagnosed with generalized lipodystrophy were, on average, younger than the patients diagnosed with partial lipodystrophy (26 ± 24 years and 48 ± 12 years, respectively).

The following figure illustrates the patients enrolled in FHA101 by lipodystrophy diagnosis:

Figure 9. FHA101 Enrollment



Source: Reviewer generated from BLA 125390 datasets

A total of 24 (86%) patients had an HbA1c 6% or greater; 75% had an HbA1c 7% or greater, and 32% had an HbA1c 9% or greater. In addition, 18 (64%) patients had a TG value 200 mg/dL or greater, eight (35%) patients had TG 350 mg/dL or greater, and five (18%) patients had TG 500 mg/dL or greater.

Of the 28 ITT patients, 27 (96%) had either a baseline HbA1c 6% or greater or TG 200 mg/dL or greater. One patient (648019) had a baseline HbA1c of 5.6% and TG of 79 mg/dL, but according to the investigator had a history of hypertriglyceridemia (TG values within 1.5 years prior to starting metreleptin ranging from 212 mg/dL to 319 mg/dL).[§§§] The patient was intolerant to statins and had fatty liver disease. Approximately 82% of the patients had HbA1c 7% or greater or fasting TG 350 mg/dL or greater.

Compared to the NIH patients, FHA101 patients had a higher mean baseline fasting leptin concentration (12.9 ng/mL versus 2.6 ng/mL), consistent with (1) the higher proportion of partial lipodystrophy patients enrolled in FHA101, and (2) leptin concentrations as inclusion criteria in the NIH trials, but not in FHA101.

[§§§] This is a protocol violation, and highlights the fluctuation in TG even off of metreleptin.

Other demographic information and baseline characteristics can be found in the table below.

Table 12. Demographics and Baseline Characteristics by Generalized and Partial Lipodystrophy, FHA101 Trial

	Generalized N=5	**Partial N=23**	**Total N=29**
Sex, n (%)			
Male	1 (20.0)	1 (4.3)	2 (7.1)
Female	4 (80.0)	22 (95.7)	26 (92.9)
Race, n (%)			
White	4 (80.0)	17 (73.9)	21 (75.0)
Black	1 (20.0)	2 (8.7)	3 (10.7)
Native American	0	1 (4.3)	1 (3.6)
Hispanic	0	1 (4.3)	1 (3.6)
Other	0	2 (8.7)	2 (7.1)
Age (years)			
Mean (SD)	25.6 (24.0)	47.5 (12.3)	43.6 (16.8)
Min, Max	9, 67	23, 67	9, 67
Age Group, n (%)			
≤ 12	2 (40.0)	0	2 (7.1)
> 12 - < 18	1 (20.0)	0	1 (3.6)
≥ 18 - ≤ 65	1 (20.0)	22 (95.7)	23 (82.1)
> 65	1 (20.0)	1 (4.3)	2 (7.1)
Lipodystrophy Type			
Congenital/Familial	1 (20.0)	21 (91.3)	22 (78.6)
Acquired	4 (80.0)	2 (8.7)	6 (21.4)
Fasting Leptin (ng/mL) †			
Mean (SD)	0.7 (0.0)	14.8 (10.3)	12.9 (10.7)
Min, Max	0.7, 0.7	1.4, 42.9	0.7, 42.9
HbA1c (%)			
Mean (SD)	8.6 (1.9)	7.9 (1.5)	8.0 (1.6)
Min, Max	5.5, 10.2	5.6, 11.1	5.5, 11.1
HbA1c Categories, n (%)			
< 6	1 (20.0)	3 (13.0)	4 (14.3)
≥ 6 to < 7	0	3 (13.0)	3 (10.7)
≥ 7 to < 9	1 (20.0)	11 (47.8)	12 (42.9)
≥ 9	3 (60.0)	6 (26.1)	9 (32.1)
Fasting TG (mg/dL)			
Mean (SD)	3248.0 (4973.5)	401.9 (537.1)	823.6 (2039.6)
Median	1099.5	255.0	257.0
Min, Max	170.0, 10623.0	66.0, 2540.0	66.0, 10623.0
Fasting TG Categories, n (%)			
< 200	1 (20.0)	3 (13.0)	4 (14.3)

≥ 200 to < 350	0	10 (43.5)	10 (35.7)
≥ 350 to < 500	1 (20.0)	2 (8.7)	3 (10.7)
≥ 500 to < 1000	0	1 (4.3)	1 (3.6)
≥ 1000	2 (40.0)	2 (8.7)	4 (14.3)
HbA1c and TG Categories, n (%)			
A1c < 6 AND TG < 200	0	1 (4.3)	1 (3.6)
A1c < 6 AND TG ≥ 200	1 (20.0)	2 (8.7)	3 (10.7)
A1c ≥ 6 AND TG < 200	1 (20.0)	7 (30.4)	8 (28.6)
A1c ≥ 6 AND TG ≥ 200	2 (40.0)	13 (56.5)	15 (53.6)
A1c ≥ 6 OR TG ≥ 200	5 (100.0)	22 (95.7)	27 (96.4)
A1c ≥ 7 OR TG ≥ 350	5 (100.0)	18 (78.3)	23 (82.1)
* Lower limit of quantitation (LLOQ) for leptin concentration is 0.7 ng/mL; values < LLOQ are reported as 0.7 ng/mL † Leptin data are not available for 6 of 28 patients			

Source: Clinical Efficacy Update, Table 35

6.1.3 Subject Disposition

NIH Trials

Seven of the nine patients enrolled in NIH study 991265 also enrolled in 200010769. As of the 11 Jul 2011 cutoff, 52 (72%) of 72 patients enrolled in the NIH trial were still actively participating.

The most common reason for withdrawal was "other" for eight (11.1%) patients (one for "stress", one for "health issues", and six were transferred to Named Patient Programs in their respective countries), followed by "noncompliance" for four (5.6%) patients.[****]

Reviewer comment: The reasons for withdrawal for "stress" and "health issues" under "other" reasons should have been considered adverse events.

Two patients withdrew because they were deemed ineligible to continue participation in the study, including one patient (90115) due to a diagnosis of peripheral T-cell lymphoma and one patient (90126) due to the investigator's assessment that the patient was no longer appropriate to continue in the study due to the need to undergo treatment for an adverse event (deep vein thrombosis).

Reviewer comment: The reasons for withdrawal for "ineligibility" should have been considered adverse events.

[****] The sponsor identified these 4 patients as: 90118, 90121, 90127, and 90146. However, Patient 90102 was also identified in the database as discontinuing due to non-compliance. This patient may have had a contributing adverse event (worsening renal function) that was not documented. See Section 7.3.5, Submission Specific Primary Safety Concerns.

A total of five patients were reported to have withdrawn due to adverse events, including deaths:

- Two patients (90147 and 90114[††††]) were withdrawn due to a non-fatal adverse event (peripheral T-cell lymphoma and proteinuria, respectively).

- Three patients experienced serious adverse events that led to death (90125, pancreatitis with a ruptured pseudocyst, leading to septic shock and subsequent cardiac arrest; 90106, renal failure and subsequent cardiac arrest; and 90158, chronic hepatic failure). These adverse events are described further in Section 7.3.1, Deaths.

Table 13. Patient Disposition for NIH Trials as of 11 July 2011

Disposition [1]	**All Patients, N=72 n (%)**
Enrolled in Study 991265	9 (12.5)
Withdrew from Study 991265	1 (1.4)
Enrolled in Study 20010769	70 (97.2)
Previously Treated in 991265 Prior to Enrolling in 20010769 [2]	7 (9.7)
Enrolled Directly into 20010769	63 (87.5)
Active in Study 20010769	52 (72.2)
Withdrew from Study 20010769	18 (25.0)
Primary Reason for Withdrawal in Studies 991265/20010769	
Other [3]	8 (11.1)
Adverse Event [4][5]	5 (6.9)
Noncompliance	4 (5.6)****
Ineligibility Determined	2 (2.8)
Consent Withdrawn	0
Administrative Decision	0
Lost to Follow Up	0

[1] Disposition of each patient is based on the data at the end of Study 991265 or as of the 11 July 2011 data cutoff for Study 20010769
[2] Includes 6 patients who completed Study 991265 and 1 patient (90105) who withdrew from Study 991265 but later enrolled into Study 20010769.
[3] Includes 6 patients who transferred to a named patient program, 1 patient due to "stress", and 1 patient due to "health issues"
[4] Includes 1 patient (90114) from Study 20010769 who was withdrawn from metreleptin due to event of proteinuria, but was re-initiated on metreleptin 3 months later, and subsequently transferred to a named patient program.
[5] Includes 3 withdrawals due to death.

Source: BLA 126390 Clinical Efficacy Update, Table 5

[††††] Patient 90114 was previously captured in Study 20010769 as discontinuation due to an adverse event. During data collection for the 120-Day Safety Update (January 2013), it was determined that the patient had not been discontinued and had resumed metreleptin therapy under study 20010769 after being off drug for 19 months. Upon resumption of dosing, the patient remained on metreleptin for 19 months and then reportedly left 20010769 to transfer into the compassionate use Named Patient Program in England.

Reviewer comments:

1. ***As noted above, some discontinuations categorized for other reasons should have been captured as adverse events leading to withdrawal.***

2. ***As of the 31 July 2009 data cut-off, five patients were reported discontinued due to non-compliance (the table above reports four).**** It was also reported that eight of nine patients in study 991265 enrolled in study 20010769 (the table above reports seven).‡‡‡‡***

As of the 11 Jul 2011 data cutoff, total exposure to metreleptin (excluding dosing gaps) for 72 NIH patients ranged from two months to approximately 11 years, with a median exposure of approximately 2.7 years, and with 60 (83%) patients having had exposure longer than one year. Forty-five patients were exposed for more than one year and up to six years, and 15 patients had more than six years of metreleptin exposure.

A total of 16 (22%) patients had dosing gaps that were excluded from exposure calculations, which varied from five days to 2,480 days. Four of the 16 patients missed more than one year of metreleptin treatment: 90105 (520 days; noncompliance), 90106 (2,480 days; withdrawal of consent after one year of metreleptin treatment, reinitiated eight years later), 90110 (803 days, due to an adverse event of 'increased LFTs' assessed as related to autoimmune hepatitis), and 90128 (742 days, noncompliance).

For the overall group of patients, the total exposure to metreleptin in the NIH trials was 280 patient-years (PY).

‡‡‡‡ This discrepancy is attributed to Patient 90103. During the compassionate use exemption (patient consented in June 2001), Patient 90103 had a serious adverse event of elevated liver function tests (December 2001 to January 2002). Although the intent was for this patient to enter Study 20010769, the investigator maintained the patient in Study 991265, but interrupted treatment to allow further assessment and a hepatology consultation. After assessment that the serious adverse event was most likely related to a concomitant medication, the patient re-initiated metreleptin treatment in March 2002 under the compassionate use exemption. Approximately three months after re-initiation of treatment, the patient had a serious adverse event of paranoia and was diagnosed with bipolar disorder (June 2002). Based on the diagnosis of bipolar disorder, the investigator concluded that the patient met an exclusion criterion for Study 20010769 (i.e., psychiatric disorder impeding competence or compliance) and therefore was not eligible to enroll into Study 20010769.

Table 14. Extent of Exposure to Metreleptin in NIH Trials with Dosing Gaps Excluded

Exposure	**All Patients N=72**
Category (years), n (%)	
≤ 0.5	4 (5.6)
> 0.5 to ≤ 1	8 (11.1)
> 1 to ≤ 2	14 (19.4)
> 2 to ≤ 3	14 (19.4)
> 3 to ≤ 4	4 (5.6)
> 4 to ≤ 5	5 (6.9)
> 5 to ≤ 6	7 (9.7)
> 6 to ≤ 7	2 (2.8)
> 7 to ≤ 8	2 (2.8)
> 8 to ≤ 9	5 (6.9)
> 9	7 (9.7)
Exposure (years)	
Mean (SD)	3.89 (3.09)
Median	2.71
Min, Max	0.2, 10.9
Total Exposure in Patient-Years	280.0
Note: Dosing gap is defined as missing one or more days of dosing	

Source: BLA 125390 Clinical Efficacy Update, Table 4

Mean exposure was greatest for CGL (4.3 y), followed by APL and FPL subtypes (3.8 y), and AGL (3.1 y). The total exposure to metreleptin in PY for each lipodystrophy subtype was as follows: CGL (138.2), FPL (76.6), AGL (49.9), and APL (15.3).

There was no systematic collection of treatment compliance data. Therefore, no analyses are available on the percent compliance with metreleptin treatment of individual patients during the treatment period.

FHA101 Trial

As of the 07 Mar 2012 data cutoff, 20 of 28 patients enrolled were still actively participating. The most common reasons for withdrawal were withdrawal of consent and adverse events (three patients each).

Reasons for withdrawal of consent were desire to get pregnant (648004), reason unspecified (648007), and travel burden coupled with lack of efficacy (648013).

Of the three withdrawals due to adverse events, two had a fatal outcome. Patient 648008 experienced a serious adverse event, 'loss of consciousness' (acute bilateral subdural hematomas after a fall), which had a fatal outcome. Patient 649001 experienced a serious adverse event of 'adenocarcinoma', which was a known pre-

existing condition prior to starting metreleptin and which had a fatal outcome. These events are discussed in Section 7.3.1, Deaths. Patient 648021 was withdrawn due to a non-serious event of muscle spasms, which was assessed by the investigator as related to treatment.

Table 15. Patient Disposition for Treatment IND FHA101 as of 07 Mar 2012

Disposition	**All Patients, N=28 n (%)**
Ongoing	20 (71.4)
Withdrew	8 (28.6)
Primary Reason for Withdrawal	
Consent Withdrawn	3 (10.7)
Adverse Event [1]	3 (10.7)
Investigator Decision	1 (3.6)
Protocol Violation	0
Lost to Follow Up	1 (3.6)
[1] Including deaths	

Source: Clinical Efficacy Update, Table 34

As of the 07 Mar 2012 cutoff for this update, total exposure to metreleptin for the 28 FHA101 patients ranged from 0.1 years to approximately three years, with a median exposure of approximately one year. The total exposure to metreleptin in the FHA101 study was 34.7 PY. Of the 28 patients, 15 patients had exposure longer than one year and six patients had exposure of two or more years.

The extent of exposure to metreleptin in FHA101 is presented in the table below.

Table 16. Extent of Exposure to Study Medication, FHA101

Exposure	**All Patients, N=28 n (%)**
Category (years), n (%)	
≤ 0.5	8 (28.6)
> 0.5 to ≤ 1	5 (17.9)
> 1 to ≤ 2	9 (32.1)
> 2 to ≤ 3	6 (21.4)
Exposure (years)	
Mean (SD)	1.24 (0.897)
Median	1.03
Min, Max	0.1, 2.9
Total Exposure in Patient-Years	34.7
Note: Dose gaps are not excluded	

Source: Clinical Efficacy Update, Table 33

Mean exposure was greatest for patients with FPL and AGL (1.3 y) followed by CGL and APL (0.6 y) subtypes. The total exposure to metreleptin in PY for each lipodystrophy subtype was as follows: FPL (27.9), AGL (5.0), APL (1.2), and CGL (0.6).

6.1.4 Analysis of Primary Endpoints

Hemoglobin A1c, Fasting Plasma Glucose, and Fasting Triglycerides

Key efficacy endpoints were considered to be HbA1c, fasting plasma glucose (FPG), and fasting TG. These endpoints, as well as fasting lipids, ALT, and AST (see Section 6.1.5), were summarized over the first 12 months of treatment.

Reviewer comment: The limitations to summarizing the data are numerous, given that individual patients may or may not "respond"[§§§§] to the intervention due to issues with compliance to metreleptin, diet, or concomitant medications in addition to changes to background therapy after starting treatment (for example, should a patient be considered a 12-month "responder" for improvement in triglycerides if she was newly started on fenofibrate prior to the 12-month visit?).

NIH Trials

Although longer-term efficacy data are available for some patients (maximum metreleptin exposure up to 11 years), the sponsor focused on results up to 12 months since this was felt to provide the best balance of the number of patients with available data and the duration of treatment.

Reviewer comment: Although I agree with the sponsor's rationale for conducting the primary efficacy evaluation on the first 12 months of data, this is problematic in cases where patients have missing data the first year, or in cases where there is a lot of variability in response over time, or when medication changes were made during the first year.

Although 60 patients had exposure exceeding one year, only 51 of those patients had efficacy data to summarize at Month 12.[*****] The nine patients missing Month 12 efficacy data had a visit prior to Month 12, and six of these had a visit subsequent to the Month 12 visit.

Reviewer comment: Given the substantial amount of missing data, I have some concern that the observed changes from baseline are an overestimate.

[§§§§] Definitions of a positive response are arbitrary, since they were not pre-specified.
[*****] One patient (90167) had exposure just shy of one year and thus not counted as exceeding one year but had data at the 12 Month visit, bringing total N at Month 12 to 52.

On average, patients treated in the NIH trials had reductions from baseline in HbA1c and FPG that were apparent at Month 4, Month 8, and Month 12, see Table 17. At Month 12, mean HbA1c decreased by 1.4% (95% CI: -1.8, -0.9) from a baseline of 8.2%, and mean FPG decreased by 41.8 mg/dL (95% CI: -65.2, -18.4) from a baseline of 169.8 mg/dL.

On average, treatment with metreleptin was associated with statistically significant reductions from baseline in fasting TG that were apparent at Month 4 and Month 12, but not at Month 8. At Month 12, the median percent change from baseline in TG was -44.8.

Table 17. Change From Baseline Month 4, 8, and 12 in HbA1c, FPG, and Fasting TG (NIH Trials)

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.

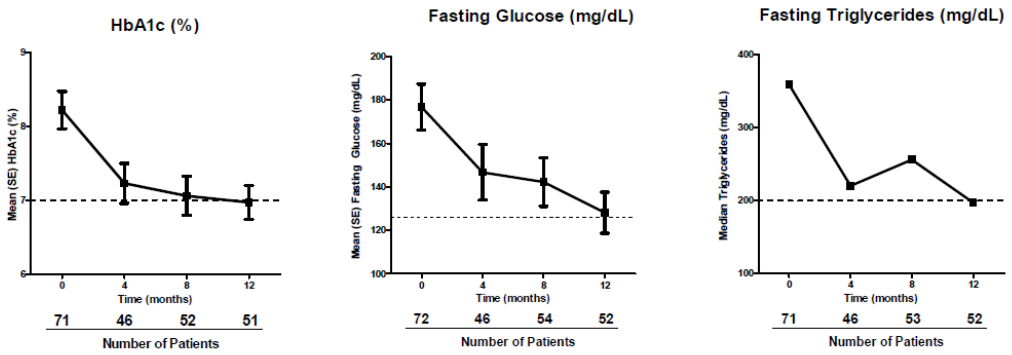
Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 8

Mean ± SE for HbA1c and FPG values and median values for fasting TG at baseline, Month 4, Month 8, and Month 12 are presented in Figure 10 for patients with observed data at each time point.

From a baseline HbA1c of 8.2 ± 0.3%, mean HbA1c values were 7.2 ± 0.3% at Month 4 and 6.9 ± 0.2% at Month 12. From a baseline FPG of 177 ± 10 mg/dL, mean FPG was 147 ± 13 mg/dL at Month 4 and 128 ± 9 mg/dL at Month 12.

TG concentrations were not normally distributed in this population and included some extreme outlying values, which have disproportionate influence on the mean values; thus median TG concentrations are plotted. From a median baseline TG of 359 mg/dL, median TG concentration was 220 mg/dL at Month 4 and 197 mg/dL at Month 12.

Figure 10. Mean (SE) HbA1c, Mean (SE) FPG, and Median Fasting TG Concentrations Over Time at Baseline and Month 4, 8, and 12 (NIH Trials)



Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 1

The sponsor considered the “completer” analysis the change from baseline in HbA1c, FPG, and fasting TG for those patients who completed at least one year of treatment and had values available for visits at baseline, Month 4, Month 8, and Month 12.

Changes from baseline in this “completer” population were of comparable magnitude and durability to those seen in the “ITT observed” population.

Table 18. Change from Baseline at Month 4, 8, and 12 in HbA1c, FPG, and Fasting TG (NIH; 12-Month Completers)

Parameter	Statistic [1][2][3]	Baseline	Month 4	Month 8	Month 12
HbA1c (%), n = 27			**Change From Baseline**		
	Mean	8.5 (1.8)	-1.2 (0.2)	-1.2 (0.3)	-1.5 (0.3)
	Median	8.7	-0.8	-1.2	-1.4
	Min, Max	5.5, 13.7	-4.0, 0.7	-4.3, 1.3	-4.5, 0.9
FPG (mg/dL), n = 30			**Change From Baseline**		
	Mean	188.4 (85.2)	-36.0 (10.0)	-36.0 (13.1)	-43.4 (15.9)
	Median	175	-34	-43	-46
	Min, Max	71, 478	-143, 125	-149, 165	-225, 271
Fasting TG (mg/dL), n = 29			**Change From Baseline**		
	Mean	1089.1 (284.6)	-470.5 (243.8)	-456.0 (317.2)	-693.5 (236.2)
	Median	471.0	-126.0	-127.0	-263.0
	Min, Max	87, 7420	-5682, 2811	-6814, 4345	-5977, 473
			Percent Change From Baseline		
	Mean	1089.1 (284.6)	-35.6 (7.6)	-22.6 (14.7)	-43.3 (7.4)
	Median	471.0	-42.0	-43.6	-51.3
	Min, Max	87, 7420	-89, 94	-92, 288	-93, 90

[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.

[3] Error is given as SD for baseline value and SE for change from baseline.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 9

Key glycemic (HbA1c) and lipid (TG) efficacy data were analyzed for both the percentage of patients achieving certain targets or achieving certain degree of improvement at specified time points. The following tables focus on the proportion of patients with clinical improvements with the most substantial baseline abnormalities. See Section 6.1.7, below, for an additional discussion of baseline metabolic derangements and improvement over time.

Table 19. Proportion of Patients Achieving HbA1c and TG Targets During Initial 12 Months of Metreleptin Treatment (NIH Trials)

Patients with Baseline HbA1c > 7% Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=46 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=39 n (%)	At Month 12 Time Point N=38 n (%)
HbA1c ≤ 7%	20 (43.5)	13 (33.3)	15 (39.5)
HbA1c ≤ 6.5%	15 (32.6)	11 (28.2)	11 (28.9)
HbA1c ≤ 6%	10 (21.7)	6 (15.4)	8 (21.1)
Decrease from baseline in HbA1c ≥ 0.5%	41 (89.1)	30 (76.9)	33 (86.6)
Decrease from baseline in HbA1c ≥ 1%	37 (80.4)	25 (64.1)	28 (73.7)
Decrease from baseline in HbA1c ≥ 2%	27 (58.7)	16 (41.0)	18 (47.4)
Patients with Baseline TG > 500 mg/dL Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=24 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=20 n (%)	At Month 12 Time Point N=19 n (%)
TG ≤ 500 mg/dL	18 (75.0)	10 (50.0)	12 (63.2)
Decrease from baseline in TG ≥ 20%	24 (100.0)	16 (80.0)	18 (94.7)
Decrease from baseline in TG ≥ 50%	23 (95.8)	12 (60.0)	15 (78.9)
Patients with Baseline TG > 1000 mg/dL Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=15 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=13 n (%)	At Month 12 Time Point N=12 n (%)
TG ≤ 1000 mg/dL	14 (93.3)	7 (53.8)	9 (75.0)
TG ≤ 500 mg/dL	9 (60.0)	3 (23.1)	6 (50.0)
Decrease from baseline in TG ≥ 20%	15 (100.0)	10 (76.9)	12 (100.0)
Decrease from baseline in TG ≥ 50%	15 (100.0)	8 (61.5)	11 (91.7)
Patients with Baseline HbA1c > 7% AND TG > 500 mg/dL Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=19 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=16 n (%)	At Month 12 Time Point N=15 n (%)
HbA1c ≤ 7% OR TG ≤ 500 mg/dL	16 (84.2)	10 (62.5)	10 (66.7)
HbA1c ≤ 7% AND TG ≤ 500 mg/dL	6 (31.6)	4 (25.0)	4 (26.7)

Source: Clinical Efficacy Update, Tables 12, 13, and 14

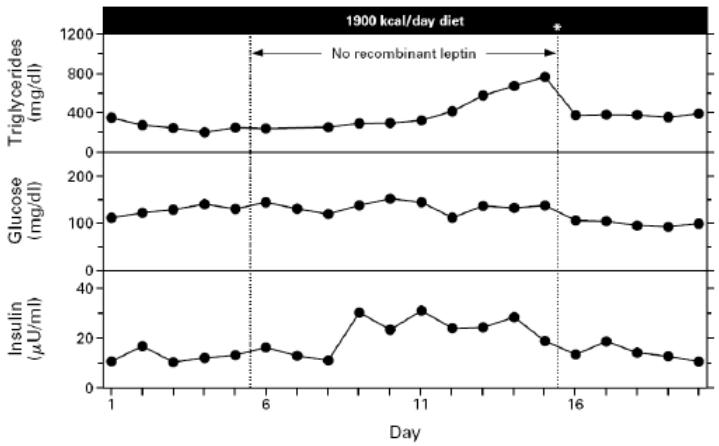
Metreleptin Dechallenge and Rechallenge

Four patients in the NIH trials were evaluated for the effects of stopping and restarting metreleptin. One patient with AGL (90101) underwent an inpatient controlled withdrawal, which was detailed in the publication by Oral, et al.[22] Two patients (90112 and 90117) with FPL underwent controlled withdrawal under the direction of the investigator to specifically test whether metreleptin was still contributing to efficacy in

addition to an insulin regimen that had been titrated to good glycemic control. A fourth patient, 90144, stopped treatment on her own during the second year of treatment and then restarted again. The details of these cases are presented below.

- Patient 90101 was a 17-year-old female with AGL who had a medical history of diabetes, severe hypertriglyceridemia (the use of plasma exchange therapy to treat this patient's severe hypertriglyceridemia is detailed in reference 21), xanthomas, and pancreatitis. The patient's baseline HbA1c and triglycerides were 8% and 7420 mg/dL, respectively. Following eight months of metreleptin treatment, metabolic control improved as evidenced by an HbA1c of 6.3% and TG of 606 mg/dL. At this time, the patient underwent a planned withdrawal of metreleptin treatment during an inpatient admission at the NIH. She was placed on a fixed caloric diet based on her reported food intake during metreleptin treatment and on her resting metabolic rate to rule out interference of changes in food intake on metabolic parameters. After five days in this controlled setting, metreleptin treatment was discontinued while all other medications were kept constant. The figure below illustrates the trajectory of TG, glucose, and insulin values over this period of time. After 15 days of withdrawal of therapy, the patient experienced nausea, vomiting, and abdominal pain consistent with pancreatitis. Resumption of metreleptin therapy returned metabolic parameters (especially TG) to pre-withdrawal concentrations.

Figure 11. Effect of Interruption of Metreleptin Treatment on Metabolic Parameters (Study 991265; Patient 90101)



Source: Clinical Efficacy Update, Figure 12 (adapted from reference 22)

Reviewer comment: This is a very compelling case of metreleptin efficacy in a patient with generalized lipodystrophy and severe insulin resistance. In particular, it is noted that she had metabolic worsening upon discontinuation of metreleptin, despite reportedly clamping energy intake, which would support an independent effect of metreleptin on insulin sensitivity independent of food

intake. Nevertheless, this is only a single case (in the very first NIH patient) and has not been replicated.

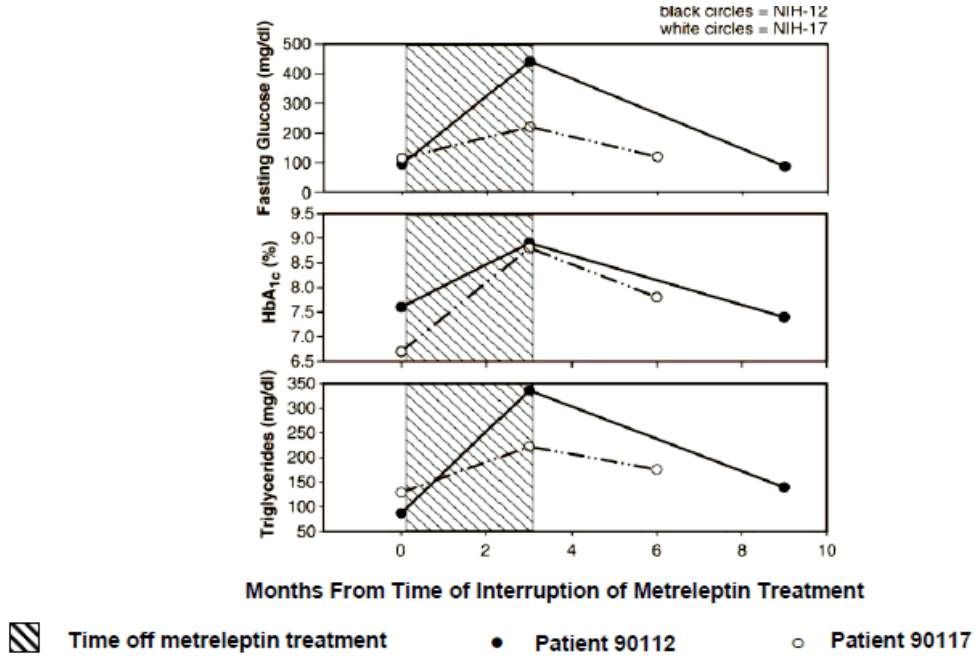
- Patient 90112 was a 64-year-old female with FPL and patient 90117 was a 45-year-old female with FPL. Both patients received metreleptin treatment for approximately 30 months prior to the controlled withdrawal. The table below demonstrates the patients' metabolic parameters prior to metreleptin withdrawal and the figure illustrates the deterioration in metabolic control during the three months that metreleptin treatment was withdrawn. Insulin and oral anti-diabetes and lipid-lowering agents were maintained at the same doses during both the three-month controlled withdrawal and re-initiation of metreleptin periods. Both patients demonstrated improvement in metabolic parameters after re-initiating metreleptin treatment.

Table 20. Individual Metabolic Parameters Prior to Controlled Withdrawal of Metreleptin: NIH Patients 90112 and 90117

Patient Number	Visit	HbA1c (%)	FPG (mg/dL)	TG (mg/dL)
900112	Baseline	9.0	232	198
64 y, F	Month 12	8.4	165	103
FPL	Month 24	6.9	117	88
	Month 30 [1]	7.6	100	87
90117	Baseline	9.7	284	550
45 y, F	Month 12	9.3	196	252
FPL	Month 24	8.0	245	177
	Month 30 [1]	6.7	123	129

[1] Last available value prior to metreleptin withdrawal.
Source: Clinical Efficacy Update, Table 18

Figure 12. Effect of Interruption of Metreleptin Treatment on Metabolic Parameters (Study 20010769; Patients 90112 and 90117)



Both patients were on metreleptin treatment for at least 12 months prior to interruption of treatment (time -= month 0).

Source: Clinical Efficacy Update, Figure 13 (adapted from reference 17)

Reviewer comment: These data were published in Park, et al.,[17] where it was noted that these patients are sisters. Therefore, whether or not these findings can be generalized to other patients with FPL is unclear. According to the table above, although there were some modest improvements, glycemic control was not substantially achieved until Month 24 (Patient 90112; note that this patient was worsening again by Month 30) or Month 30 (Patient 90117). In addition, insulin was started at Month 24 in both patients, approximately six months before metreleptin was temporarily withdrawn. Therefore, the pre-withdrawal improvements in HbA1c were confounded and difficult to definitively attribute to metreleptin. See below for continued changes in HbA1c over time:

Table 21. HbA1c (%) Over Time[1]; Patients 90112 and 90117

Patient	Baseline	Month 4	Month 8	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72	Month 84
90112	9	8.5	7.8	8.4	6.9	8.7	7.4	7.2	7.5	6.7
90117	9.7	8.6	8.8	9.3	8	7.8	8.5	9.6	10.9	

[1] Note that Month 30 from the above table is missing in this table generated from datasets

Source: Reviewer-generated from BLA datasets (Clinical Efficacy Update, dlabs-2.xpt)

- Patient 90144 initiated metreleptin at the age of 10 years. At the time of enrollment, she was diagnosed as having APL; however, as her disorder progressed the patient's loss of body fat was assessed by the investigator to be more consistent with AGL. By report, she was initiated on treatment based on significant insulin resistance, hypertension, hypertriglyceridemia, and elevated transaminases and evidence of hepatic steatosis on ultrasound. Baseline HbA1c was 4.6%, FPG 74 mg/dL, TG 108 mg/dL, ALT 90 U/L, and AST 48 U/L. After two years of metreleptin treatment (the patient was 12 years of age), she discontinued treatment due to lack of changes in physical appearance. Metabolic parameters had generally remained stable on metreleptin treatment (i.e., no increase from baseline). Following the Year 2 visit, the patient discontinued metreleptin treatment and did not return to the NIH for nine months. At this visit, the patient's metabolic deterioration was evident including development of overt diabetes (HbA1c 7.5%, FPG 232 mg/dL), severe hypertriglyceridemia (622 mg/dL), increased ALT (229 U/L) and AST (91 U/L), elevated urine protein:creatinine ratio (previously normal), and lack of pubertal progression. The patient re-initiated metreleptin treatment and six months after re-starting metreleptin (i.e, the first follow up visit), metabolic abnormalities had improved (HbA1c 4.8%, FPG 85 mg/dL, TG 96 mg/dL, ALT 61 U/L, AST 18 U/L), and the patient also had significant pubertal progression to Tanner stage IV. The NIH investigators noted that the patient's dramatic worsening while off metreleptin may have been exaggerated by the physiologic insulin resistance of puberty, as she was mid-pubertal during that time.

Reviewer comment: The narrative (as well as the publication regarding this patient's stopping and restarting metreleptin therapy[23]) did not mention that she was also started on insulin upon restarting metreleptin; see Table 22. In addition, the confounding of puberty makes this case difficult to interpret.

Table 22. Changes in HbA1c and Diabetes Medications Over Time, NIH Patient 90144

Visit	Baseline	Month 8	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 42 (follow-up?)
Study Day	-1	178	371	535	604	863	1064	1218	1274
HbA1c (%)	4.6	4.5	4.8	5	5.3	7.5	4.8	5.2	4.9
Insulin (µIU/mL)	57.6			114		200	40.5	51.8	49.5
Glucose (mg/dL)	80	94	85	93	108	235	86	94	92
Diabetes medications		Started on metformin 250 mg QD study day 179; increased to 500 mg BID study day 247	Metformin increased to 1000 mg BID on day 372	Metformin 1000 mg BID	Metformin 1000 mg BID	Metformin 1000 mg BID + Insulin sliding scale started	Metformin 1000 mg BID + Insulin sliding scale	Metformin 1000 mg BID (Insulin sliding scale stopped)	Metformin 1000 mg BID
Metreleptin	Start (day 1)	Continue	Continue	Continue	Stop	Restart	Continue	Continue	Continue

Source: Reviewer generated table; datasets: NIH20010769 dconme-2.xpt and NIH20010769 dlabs-2.xpt

Concomitant Medications

Because any alterations in background therapies to treat the metabolic complications of lipodystrophy could confound the efficacy results, the efficacy of metreleptin by concomitant medication was analyzed; analyses were focused on the first 12 months of treatment.

Reviewer comment: Note that metreleptin for lipodystrophy originally obtained fast-track designation (2001) as a result of demonstration of reduction or discontinuation of anti-hyperglycemic medications seen in very preliminary data from NIH trial 991265 (as described in reference 22). Therefore, the capture and reporting of concomitant medications is considered critical to assess the efficacy of metreleptin therapy.

Diabetes Medications

According to the NIH protocol, once patients are enrolled in the trial, other forms of glucose-lowering therapy are not to be increased for at least the first four months. Patients are to be maintained on a stable regimen for six to eight weeks prior to enrollment. Study physicians are to use their best clinical judgment to decrease the dose or frequency of these medications if hypoglycemia occurs. In the absence of hypoglycemia, physicians are to maintain patients on stable glucose-lowering therapies so that the only variable will be increasing dose of metreleptin.

In the NIH trials, 88% of patients were receiving at least one anti-hyperglycemic medication at baseline.

Table 23. Proportion of Patients Receiving Baseline Diabetes Concomitant Medications (NIH Trials)

	All Patients N=72
Receiving Diabetes Medication at Baseline	63 (87.5)
Insulin alone	14 (19.4)
Insulin + metformin	18 (25.0)
Insulin + TZD	2 (2.8)
Metformin alone	14 (19.4)
TZD alone	3 (4.2)
≥ 2 oral agents	12 (16.7)

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 17

Given the 12-month data cut was the primary analysis for the key efficacy assessments outlined in previous sections, the sponsor conducted concomitant diabetes medication analyses focused on the initial 12 months of treatment.

At each analysis time point, patients were classified as to whether their diabetes medications had:

- Stopped (no diabetes medications being taken)
- Decreased (total daily dose decreased but at least one diabetes medication was still being taken)
- Remained Stable (total daily dose was unchanged)
- Increased (total daily dose increased)
- Insulin Added (total daily dose of oral agent(s) was unchanged but insulin added as a new medication)
- Oral Agent Added (total daily dose of baseline insulin and/or oral agents was unchanged but an oral agent added as a new medication)
- Indeterminate (e.g., total daily dose at baseline or at analysis time point could not be determined; or a change in oral diabetes medications (such as metformin stopped while pioglitazone started); or insulin daily dose decreased but oral agent daily dose increased)

Additionally, patients not taking diabetes medications at baseline were classified into the following categories, based on medications being taken at the analysis time point:

- Continued to not take diabetes medications

- Started taking insulin
- Started taking an oral agent

The sponsor also conducted a summary of efficacy according to certain medication subgroups at the Month 4 and Month 12 time points.

Table 24. Change from Baseline to Month 4 and Month 12 by Diabetes Medication Category: Patients with 4 and 12 Month Exposure and Who Received Diabetes Medications at Baseline and/or Month 4 and 12 (NIH Trials)[†††††]

Baseline Medication Category	N	Discontinued	Decreased	Unchanged	Increased	Insulin Added	Oral Added	Indeterminate
On DM Meds at BL								
Month 4								
1 Oral Agent Only	16	2 (12.5)	-	14 (87.5)	-	-	-	-
2 or More Oral Agents	12	2 (16.7)	3 (25.0)	7 (58.3)	-	-	-	-
Insulin Alone	13	2 (15.4)	3 (23.1)	5 (38.5)	1 (7.7)	-	-	2 (15.4)
Insulin + Oral Agent [1]	19	2 (10.5)	4 (21.1)	8 (42.1)	2 (10.5)	-	-	3 (15.8)
Total	**60**	**8 (13.3)**	**10 (16.7)**	**34 (56.7)**	**3 (5.0)**	**0 (0.0)**	**0 (0.0)**	**5 (8.3)**
Month 12								
1 Oral Agent Only	15	2 (13.3)	1 (6.7)	10 (66.7)	-	1 (6.7)	-	1 (6.7)
2 or More Oral Agents	12	3 (25.0)	2 (16.7)	2 (16.7)	1 (8.3)	1 (8.3)	2 (16.7)	1 (8.3)
Insulin Alone	8	4 (50.0)	1 (12.5)	2 (25.0)	-	-	-	1 (12.5)
Insulin + Oral Agent [1]	18	4 (22.2)	6 (33.3)	2 (11.1)	2 (11.1)	-	-	4 (22.2)
Total	**53**	**13 (24.5)**	**10 (18.9)**	**16 (30.2)**	**3 (5.7)**	**2 (3.7)**	**2 (3.7)**	**7 (13.2)**
Not on DM Meds at BL								
Month 4	**2**					-	**2 (100.0)**	-
Month 12	**2**					-	**2 (100.0)**	-

[1] For the category Insulin + Oral Agent, the change from baseline is determined by insulin dose only. It should be noted that all patients in this category were only on 1 oral agent.

Source: Clinical Efficacy Update Table 24

Reviewer comment: I was unable to reproduce this table. The per patient medication data available for review was provided in a separate submission upon request, and at least one discrepancy was noted between the analyses provided in the Clinical Efficacy Update and results from the per patient data (by my assessment, a patient who was considered "unchanged" should have been considered "oral added"). Despite some challenges, I have attempted to determine the individual patients who make up the Month 12 findings. Of the 53 patients who were on anti-hyperglycemic medications at baseline and had 12 month data, 33 patients had generalized lipodystrophy (note that 48 generalized lipodystrophy patients were enrolled overall) and 20 patients had partial lipodystrophy (note that 24 partial lipodystrophy patients were enrolled overall).

[†††††] Potential protocol violations: 3 patients on anti-hyperglycemic medications at baseline who had doses increased by Month 4; 2 patients not on diabetes medications at baseline started on new medications by Month 4

According to my manual review of the medication data:

- ***Of the 13 patients who <u>discontinued</u> anti-hyperglycemic medications by Month 12, 12 had generalized lipodystrophy and one had partial lipodystrophy***
- ***Of the 10 patients who had their dose(s) <u>decreased</u> by Month 12, five patients had generalized lipodystrophy and five had partial lipodystrophy***
- ***Of the 15 patients whose doses were <u>unchanged</u>, 10 patients had generalized lipodystrophy and five had partial lipodystrophy***
- ***Of the three patients who had doses <u>increased</u>,‡‡‡‡‡ one patient had generalized lipodystrophy and two had partial lipodystrophy***
- ***Of the five patients who had <u>oral anti-hyperglycemic medications added</u>,‡‡‡‡‡ two had generalized lipodystrophy and three had partial lipodystrophy***
- ***Of the two patients who had <u>insulin added</u>,‡‡‡‡‡ both had partial lipodystrophy***
- ***Of the seven patients in the <u>indeterminate</u> category,‡‡‡‡‡ four had generalized lipodystrophy and three had partial lipodystrophy***

Descriptive analyses of changes in total daily insulin dose at Months 4 and 12 were also conducted; see table below.

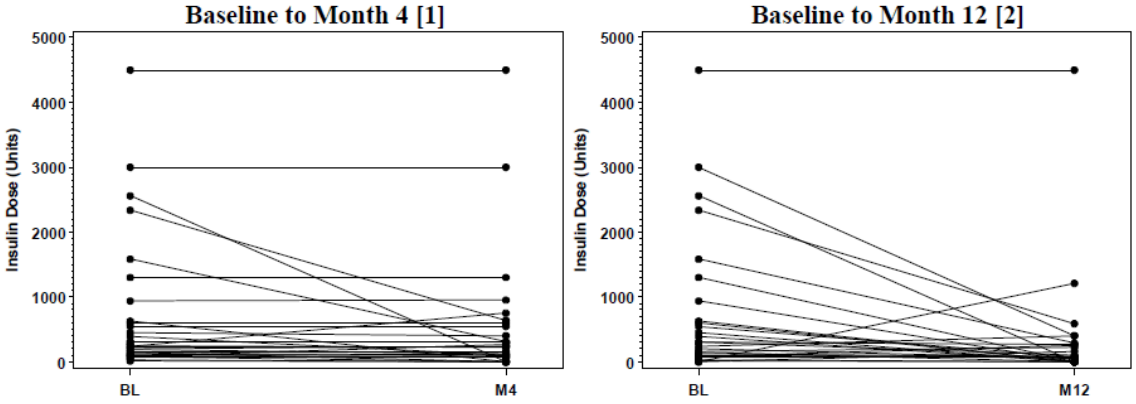
‡‡‡‡‡ The sponsor reports that doses were generally held stable during the first year, except when decreases were necessary to avoid hypoglycemia; however, this was not the case for 14% of patients; in addition, those 10% in the indeterminate category may have had medication changes in the first year in order to optimize glycemic management.

Table 25. Total Daily Insulin Dose at Baseline, Month 4, and Month 12: Patients Who Received Insulin (NIH; ITT Population Observed Data)

	Baseline [1]	**Month 4 [2]**
Received Insulin at Baseline or Month 4 (n)	30	
Mean daily insulin dose (U)	724.1	519.0
Median daily insulin dose (U)	272.5	240.0
Min, Max	12.0, 4500.0	0.0, 4500.0
	Baseline [1]	**Month 12**
Received Insulin at Baseline or Month 12 (n)	26	
Mean daily insulin dose (U)	790.5	335.6
Median daily insulin dose (U)	300.0	74.5
Min, Max	0.0, 4500.0	0.0, 4500.0
[1] 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. [2] Two of the 32 patients identified in Table 24 receiving insulin alone or an insulin + oral agent at Month 4 had doses assessed as indeterminate and therefore not included in this table.		
Source: Clinical Efficacy Update Table 25		

Total daily insulin doses for individual patients from baseline to Month 4 and from baseline to Month 12 are shown in Figure 13.

Figure 13. Individual Total Daily Insulin Dose at Baseline, Month 4, and Month 12: Patients Who Received Insulin (NIH; ITT Population Observed Data)



[1] N = 30 for Month 4. Two of the 32 patients identified in Table 24 receiving insulin alone or an insulin + oral agent at Month 4 had doses assessed as indeterminate and therefore not included in this figure.
[2] N = 26 for Month 12.
Source: Clinical Efficacy Update Figure 18

Specific findings regarding individual patients include the following:

- One patient (90132, 18-year-old female with APL) had a notable increase in insulin dose at Month 12. The patient was not on insulin at baseline and had insulin added at Month 12.§§§§§
- Five patients had marked reductions (greater than 1000 U/day) in insulin dose.******
- Patient 90122 (14-year-old female with CGL) was on a very high dose of insulin for three years prior to entry in the study (4500 U/day). This patient's insulin doses remained stable through Month 12 of metreleptin treatment, while HbA1c improved from a baseline of 13.7% to 9.2%. The insulin dose was reduced to 3000 U/day after about 16 months of treatment, and reduced even further to 175 U/day after about 2 years of treatment. Despite these reductions in insulin dose, the patient's HbA1c continued to decrease. The patient's HbA1c was 8.2% and 5.6% at Month 21 and Month 36, respectively.

Reviewer comment: It is notable that it took this patient three years to achieve glycemic control. While metreleptin may have played a role in the improvement, it is not clear if additional interventions may have contributed to the observed changes over time.

Lipid Medications

Similar to the diabetes medications analyses, the sponsor conducted concomitant lipid medication analyses focused on the initial 12 months of treatment. During the first 12 months of the NIH trials, concomitant lipid medications were generally held stable per protocol.

In the NIH trials, 50% of patients were receiving at least one lipid-lowering medication at baseline.

§§§§§ The HbA1c and FPG of Patient 90132 went from 6.3% and 243 mg/dL at baseline, respectively, to 5.7% and 135 mg/dL (Month 4), 6.7% and 270 mg/dL (Month 8), and 6% and 57 mg/dL (Month 12).

****** One of these patients (90163) was actually reported in the data listings to have started insulin (3000 U total daily dose) on the first day on metreleptin therapy. It is unclear if she was on insulin prior to starting the trial, but if so, it was not reported.

Table 26. Proportion of Patients Receiving Baseline Lipid-Lowering Concomitant Medications (NIH; ITT Population)

	All Patients N=72
Receiving Lipid Medication at Baseline	**36 (50.0)**
Monotherapy	**26 (36.1)**
Fibrate	17 (23.6)
Statin	3 (4.2)
Fish Oil	6 (8.3)
≥ 2 Medications	**9 (12.5)**
Fibrate + Statin	5 (6.9)
Fibrate + Fish Oil	2 (2.8)
Statin + Fish Oil	1 (1.4)
Fibrate + Statin + Fish Oil	1 (1.4)
Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 20	

During the NIH trials, the majority of patients maintained their lipid-lowering medication regimen from baseline to Month 4 (88%) and from baseline to Month 12 (72%). Fibrates are commonly-used medications to treat hypertriglyceridemia (the primary lipid abnormality in patients with lipodystrophy); therefore, the sponsor's analyses focused on changes in fibrate dose.

Table 27. Change from Baseline to Month 4 and Month 12 by Lipid-Lowering Category: Patients with 4 and 12 Month Exposure and Who Received Lipid-Lowering Medications at Baseline and/or Month 4 and 12 (NIH; ITT Population Observed Data)

Baseline Medication Category	N	Stopped	Decreased	Unchanged	Increased	Fibrate Added	Non-Fibrate Added	Indeterminate
On Lipid-Lowering Meds at BL								
Month 4								
Fibrate Alone	16	1 (6.3)	-	15 (93.8)	-	-	-	-
Fibrate Combo [1]	8	-	-	7 (87.5)	-	-	-	1 (12.5)
Non-Fibrate	9	-	1 (11.1)	7 (77.8)	-	1 (11.1)	-	-
Total	**33**	**1 (3.0)**	**1 (3.0)**	**29 (87.9)**	**0 (0.0)**	**1 (3.0)**	**0 (0.0)**	**1 (3.0)**
Month 12								
Fibrate Alone	15	2 (13.3)	-	13 (86.7)	-	-	-	-
Fibrate Combo [1]	6	-	2 (33.3)	3 (50.0)	1 (16.7)	-	-	-
Non-Fibrate	8	-	1 (12.5)	5 (62.5)		2 (25.0)	-	-
Total	**29**	**2 (6.9)**	**3 (10.3)**	**21 (72.4)**	**1 (3.4)**	**2 (6.9)**	**0 (0.0)**	-
Not Lipid-Lowering Meds at BL								
Month 4	1					-	1 (100.0)	-
Month 12	2					2 (100.0)	-	-

[1] The change from baseline is determined by the fibrate dose only.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 26

Reviewer comment: I was unable to reproduce this table. Key findings at Month 12 that I was able to identify (by manual review) include:

- ***The two patients who <u>stopped</u> treatment with fibrate both had generalized lipodystrophy***
- ***The patient whose <u>dose of fibrate was increased</u> had partial lipodystrophy***
- ***All five patients who had a <u>lipid-lowering drug added</u> (fibrate or non-fibrate) had partial lipodystrophy***

At Months 4 and 12, the mean fibrate dose decreased, while the median dose remained constant.

Table 28. Total Daily Fibrate Dose at Baseline, Month 4, and Month 12: Patients Who Received Fibrates (NIH; ITT Population Observed Data)

	Baseline [1]	**Month 4**
Received Fibrate at Baseline or Month 4 (n)	25	
Mean daily fibrate dose (mg)	375.3	341.7
Median daily fibrate dose (mg)	145.0	145.0
Min, Max	0.0, 2400.0	0.0, 2400.0
	Baseline [1]	**Month 12**
Received Fibrate at Baseline or Month 12 (n)	25	
Mean daily fibrate dose (mg)	355.1	220.6
Median daily fibrate dose (mg)	145.0	145.0
Min, Max	0.0, 2400.0	0.0, 2400.0
[1] 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.		
Source: Clinical Efficacy Update Table 27		

Trial FHA101

As the majority of patients in this trial up to the 2012 data cutoff had partial lipodystrophy, the sponsor summarized the patients with generalized lipodystrophy separately, and by individual patient.

Table 29. Individual Efficacy Data: Patients With Generalized Lipodystrophy, FHA101

Patient Number	Visit	HbA1c (%)	FPG (mg/dL)	TG (mg/dL)	ALT (U/L)	AST (U/L)
648001	Baseline	9.1	262	10,623	27	20
	Month 12	7.8	133	140	34	19
648016	Baseline	5.5	110	354	419	208
	Month 12	4.7	77	30	25	35
648022	Baseline	10.2	420	1,845	259	145
	Month 6 [1]	4.5	78	502	19	20
649001	Baseline	9.9	188	554	21	24
	Month 1 [1]	9	161	320	18	27
677002	Baseline	8.4	274	170	51	47
	Month 6 [1]	11.5	239	341	58	51

[1] Last available post-baseline value.
[2] Patient 677002 was withdrawn from the protocol (investigator decision, FHA101 Appendix 3.1) due to family conflict, personal issues, missed appointments and intermittent noncompliance

Source: Clinical Efficacy Update, Table 37

Reviewer comment: Contrast the information in the above table with the data presented below for Patient 648001. Although the following data are from the immunogenicity report in the BLA (note that no leptin neutralizing activity was reported), the change in efficacy over time in this patient was noted that is not included in the table above. There were reportedly compliance issues in this patient after Month 18, although interestingly, reported leptin concentrations do not reflect that.

Table 30. Metabolic Parameters Over the Time of Metreleptin Treatment: Patient 648001 (9 yo F AGL)

Visit	Baseline	Mo 3	Mo 6	Mo 12	Mo 15	Mo 20	Mo 24	Mo 27	Mo 32	Mo 35
Leptin (ng/mL)	0.7	0.7	0.7	1.6	0.7	26.3	25.2	41.3	4.4	8.9
TG (mg/dL)	10623	1059	3901	140	123	392	10851	2036	590	2452
Glucose (mg/dL)	262	277	273	133	155	87	220	163	128	131
HbA1c (%)	9.1	8.4	9.2	7.8	7.2	8.7	9.8	9.7	9.0	9.1

Source: Clinical Addendum, FHA101, Appendix 5.3.2; FHA101 datasets, DCLINLAB

Two of the patients without 12-month data discontinued prematurely: Patient 649001, a 67-year-old female with AGL died from adenocarcinoma, and Patient 677002, a 25-year-old female with CGL was withdrawn from the protocol due to family conflict, personal issues, missed appointments, and intermittent noncompliance. Patient 648022, a 16-year-old female with AGL, had markedly elevated HbA1c and TG at baseline, and demonstrated improvement by Month 6, which was last available post-baseline visit, see Table 29 above. Of note, these changes occurred despite discontinuing insulin and pioglitazone.

By contrast, the results in patients with partial lipodystrophy were modest, which supports this finding in the NIH trials.

Table 31. Change From Baseline to Month 12 in HbA1c, FPG, and Fasting TG: Patients With Partial Lipodystrophy, FHA101

Parameter	Statistic [1][2][3]	Month 3	Month 6	Month 9	Month 12
HbA1c (%)	**N**	19	14	15	8
	Baseline Mean (SD)	7.9 (1.6)	7.7 (1.5)	8.0 (1.7)	8.7 (1.7)
	Change from Baseline				
	Mean (SE)	-0.2 (0.3)	-0.2 (0.4)	-0.3 (0.4)	-0.9 (0.6)
	Median	0.0	-0.1	-0.1	-0.1
	Min, Max	-4.5, 1.2	-4.9, 2.6	-4.8, 3.3	-4.7, 0.4
	95% CI	-0.8, 0.4	-1.2, 0.7	-1.2, 0.6	-2.3, 0.6
FPG (mg/dL)	**N**	18	14	14	8
	Baseline Mean (SD)	138.9 (51.3)	146.4 (53.1)	141.9 (51.5)	172.9 (49.5)
	Change from Baseline				
	Mean (SE)	24.4 (25.0)	-26.4 (13.8)	7.4 (23.2)	-42.0 (22.4)
	Median	-1.0	-25.5	6.5	-33.5
	Min, Max	-140, 325	-144, 74	-143, 175	-127, 43
	95% CI	-28, 77	-56, 3	-43, 58	-95, 11
Fasting TG (mg/dL)	**N**	18	14	14	8
	Baseline Mean (SD)	310.3 (298.2)	333.3 (336.5)	292.0 (291.5)	338.8 (255.0)
	Baseline Median	251.0	227.0	227.0	322.5
	Change from Baseline				
	Mean (SE)	-37.8 (63.6)	-60.9 (63.2)	-19.4 (71.8)	-119.8 (84.1)
	Median	-16.5	-11.5	3.0	-81.0
	Min, Max	-807, 388	-844, 130	-772, 519	-644, 129
	Percent Change from Baseline				
	Mean (SE)	12.3 (18.1)	5.1 (13.3)	31.2 (35.8)	-23.1 (15.0)
	Median	-9.8	-4.4	1.5	-32.4
	Min, Max	-65, 193	-68, 120	-62, 481	-70, 39
	95% CI	-25.9, 50.6	-23.5, 33.7	-46.1, 108.5	-58.5, 12.4

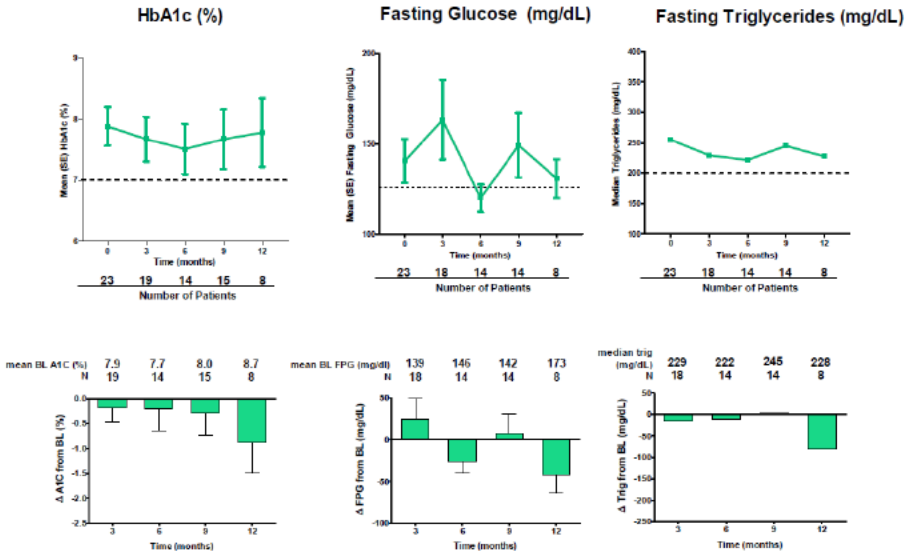
[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time 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] 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, Table 38

Figure 14. Key Efficacy Parameters over Time and by Change From Baseline to Month 3, 6, 9, and 12: Patients with Partial Lipodystrophy; FHA101



[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.

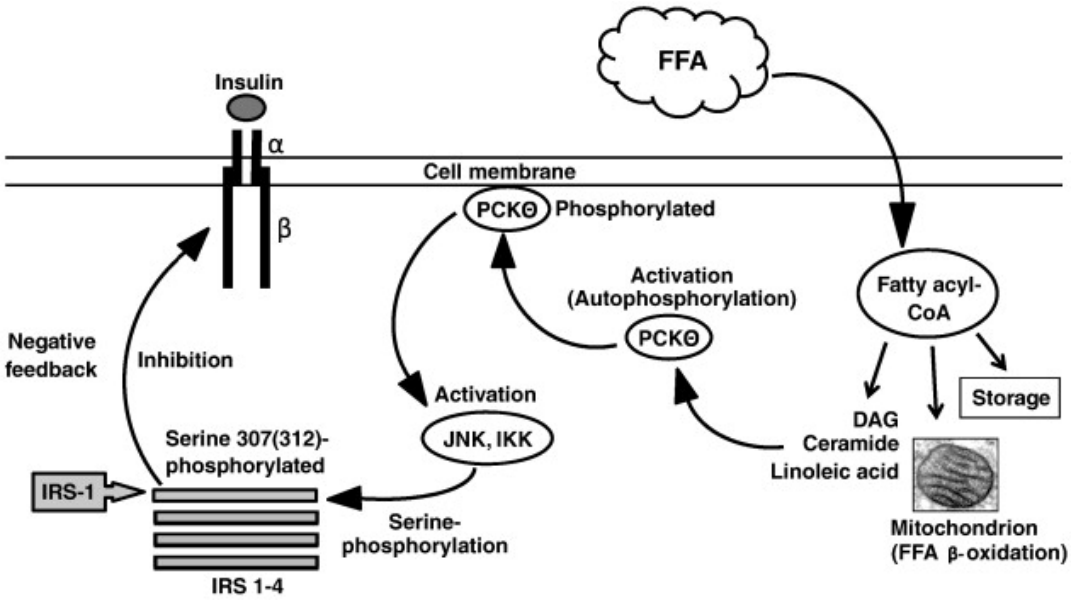
Source: Clinical Efficacy Update, Figure 26

Reviewer comment: There are very limited data at the 12-month time point (n = 8); therefore results at Month 12 should be interpreted with caution. Note that the patients with Month 12 data have the highest mean baseline HbA1c and fasting glucose.

6.1.5 Analysis of Secondary Endpoints

Given the research orientation of these trials, no endpoints were formally considered "secondary"; however, additional endpoints of interest from the NIH trials are presented in this section. Some of these endpoint assessments, for example, circulating free fatty acids (FFAs) and measures of insulin resistance, describe and refine the potential mechanisms whereby patients with lipodystrophy develop co-morbid conditions and how leptin may affect the disease. In lipodystrophy, in which storage of triglycerides is disrupted, circulating FFAs become pathogenic. In the following figure from Capurso[24], the mechanism by which excess FFAs (in this case, in the metabolic syndrome) leads to insulin resistance is described. The authors note that when fatty acid flux exceeds the capacity of oxidation or storage, fatty acids and intermediates of fatty acid metabolism accumulate and dysregulate insulin signaling by serine phosphorylation of insulin receptor substrate (IRS)-1.

Figure 15. Role of Free Fatty Acids in Insulin Receptor Signaling



Source: Reference 24

The results for completed NIH trial 991265 and ongoing trial 20010769 based on an earlier data cut (31 Jul 2009) were presented in the original BLA submission in December 2010. The sponsor provided an Efficacy Update with data based on a more recent data cut (July 2011) that includes more limited efficacy data.

While the following endpoint data were collected at the study site for all patients, some of the data are available for 29 patients from the 2005 data cut only and therefore, where applicable, the analyses were conducted for this subpopulation.

Reviewer comment: Given that the population, metabolic abnormalities, and response to therapy could be different for the first 29 patients versus the entire 72 patient population, these results should be interpreted with caution.

The original study report for the NIH trials includes the following secondary endpoints:

- Fasting lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and free fatty acids)
- Fasting insulin
- Glucose, insulin, and free fatty acid profiles from the OGTT
- Glucose profiles from the insulin tolerance test
- Glucose and insulin profiles from the IVGTT
- The usage of diabetes and lipid medications
- Resting metabolic rate

- Hepatic: liver volume, ALT, AST, liver biopsy results where available
- Endocrine
    - Hypothalamic-pituitary-gonadal axis: LH, FSH, estradiol, testosterone
    - Hypothalamic-pituitary-thyroid axis: TSH, T3, T4
    - Hypothalamic-pituitary-adrenal axis: cortisol, ACTH
- Anthropometric measures

Other Lipids

Mean LDL-C was mildly elevated at baseline (118 mg/dL) with a mean decrease of 17 mg/dL at Month 4 and 28 mg/dL at Month 12. Mean HDL-C was low at baseline (32 mg/dL) and there were small mean decreases (-1.2 mg/dL at Month 4 and -0.7 at Month 12). Some of the reduction in total cholesterol was thought to be due to the decrease in TG concentrations following metreleptin treatment since TG-rich particles, such as very low density lipoprotein (VLDL) particles, also contain cholesterol.

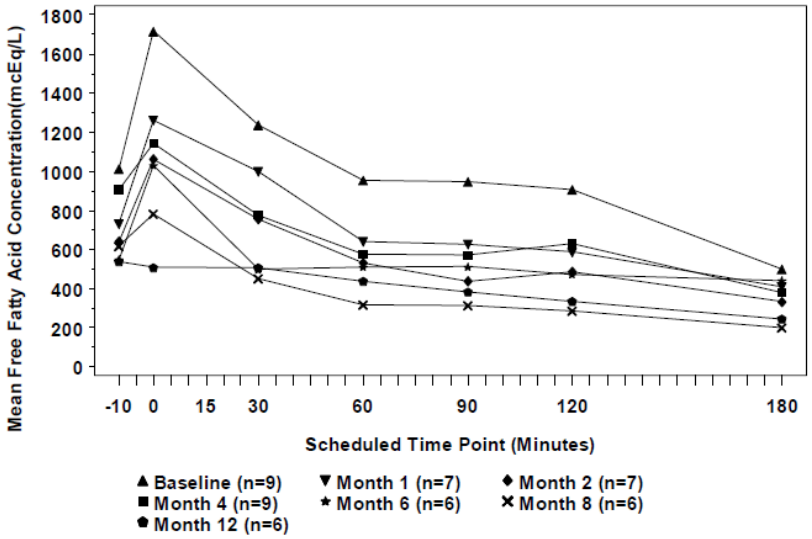
Table 32. Mean (SE) Change from Baseline to Month 12 in Fasting Lipids, NIH Trials

Parameter	Statistic[1][2][3]	Month 4	Month 8	Month 12
Free Fatty Acids (mcEq/L)	N	35	39	36
	Baseline mean (SD)	804.7 (685.7)	767.0 (685.1)	719.6 (699.8)
	Change from baseline			
	Mean (SE)	-358.7 (114.9)	-247.1 (107.1)	-252.9 (117.9)
	Median	-159.00	-104.00	-151.50
	Min, Max	-2959.0, 828.0	-2725.0, 957.0	-2596.0, 1514.0
	95% CI	-592.2, -125.2	-463.9, -30.2	-492.32, -13.57
LDL Cholesterol (mg/dL)	N	30	33	32
	Baseline mean (SD)	117.9 (49.1)	109.2 (55.5)	116.8 (49.4)
	Change from baseline			
	Mean (SE)	-17.3 (8.7)	-26.1 (7.7)	-27.6 (8.1)
	Median	-7.00	-19.00	-18.00
	Min, Max	-158.0, 105.0	-176.0, 45.0	-168.0, 54.0
	95% CI	-35.0, 0.4	-41.8, -10.4	-44.2, -11.0
HDL Cholesterol (mg/dL)	N	44	50	50
	Baseline mean (SD)	32.0 (9.9)	30.7 (9.4)	31.6 (9.0)
	Change from baseline			
	Mean (SE)	-1.16 (0.9)	-0.20 (1.0)	-0.72 (1.0)
	Median	-1.00	-1.50	-1.00
	Min, Max	-12.0, 14.0	-18.0, 17.0	-19.0, 16.0
	95% CI	-2.9, 0.6	-2.3, 1.9	-2.7, 1.2
Total Cholesterol (mg/dL)	N	46	53	52
	Baseline mean (SD)	240.4 (124.0)	235.6 (156.03)	235.9 (124.8)
	Change from baseline			
	Mean (SE)	-70.54 (18.0)	-64.6 (17.8)	-67.7 (13.9)
	Median	-47.00	-42.00	-43.00
	Min, Max	-475.0, 312.0	-628.0, 60.0	-531.0, 57.0
	95% CI	-106.8, -34.3	-100.3, -28.9	-95.7, -39.8

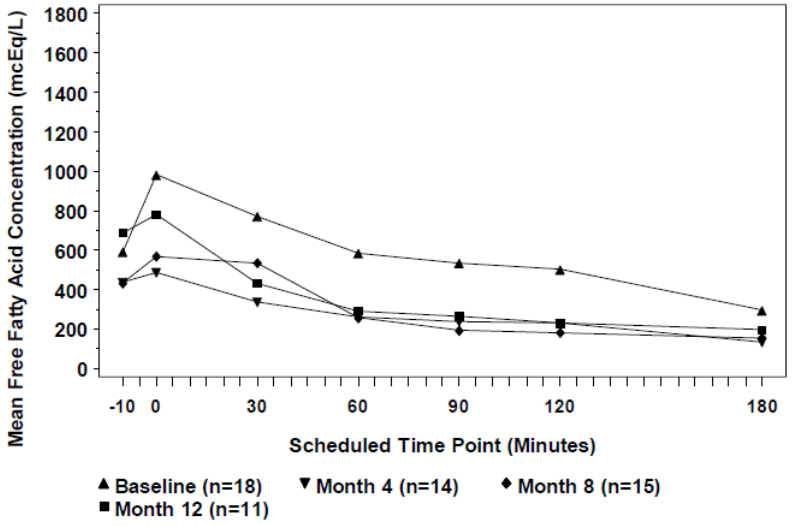
[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time 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.

Source: Clinical Efficacy Update, Table 19

Figure 16. Mean Free Fatty Acid Profile by Visit from the Oral Glucose Tolerance Test; ITT Patients in Study 991265 (Top, N=9) and Study 20010769 (Bottom, N=20), 2005 Datacut



Notes: - Cohort 1 includes subjects who initiated metreleptin treatment in Study 991265.
- Baseline profile is defined as the last available profile before the subject received the first injection of metreleptin.
- Only the visits at which at least 5 subjects had data were displayed.
- Time point 0 refers to the time when oral glucose solution was administered for oral glucose tolerance test.



Notes: - Cohort 2 includes subjects who initiated metreleptin treatment in Study 20010769.
- Baseline profile is defined as the last available profile before the subject received the first injection of metreleptin.
- Only the visits at which at least 10 subjects had data were displayed.
- Time point 0 refers to the time when oral glucose solution was administered for oral glucose tolerance test.

Source: NIH Study Report Body, Supporting Data Summaries 2.6.3.3.1 and 2.6.3.3.2

Insulin Sensitivity

Fasting Insulin

Fasting insulin is a marker of insulin resistance. Fasting insulin data are only available for the 2005 data cut (n = 29). The data are further limited because fasting insulin concentrations were only evaluated in those patients who were not receiving concomitant insulin therapy. Decreases in mean fasting insulin concentrations were observed at Months 4 and 8 of metreleptin treatment and a mean increase was observed at Month 12.

Table 33. Mean Change From Baseline in Fasting Insulin Concentrations in Patients Who Were Not Treated With Insulin During the NIH Trials, 2005 Data Cut (N = 10)

	Statistics	Month 4	Month 8	Month 12
Fasting Insulin(µIU/mL)	**N**	10	8	8
	Baseline Mean (SD)[1]	28.1 (24.6)	27.0 (26.4)	27.0 (26.4)
	Change from Baseline			
	Mean (SE)	-3.0 (4.6)	-8.0 (6.5)	2.9 (4.5)
	Median	-3.9	-3.8	-0.3
	Min, Max	-19.0, 32.5	-48.0, 13.6	-18.6, 22.7

SD = standard deviation; SE = standard error; OGTT = oral glucose tolerance test

[1] 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. If baseline value from insulin test was missing, the baseline fasting insulin value from the OGTT test was used.
Source: NIH Study Report, Table 17

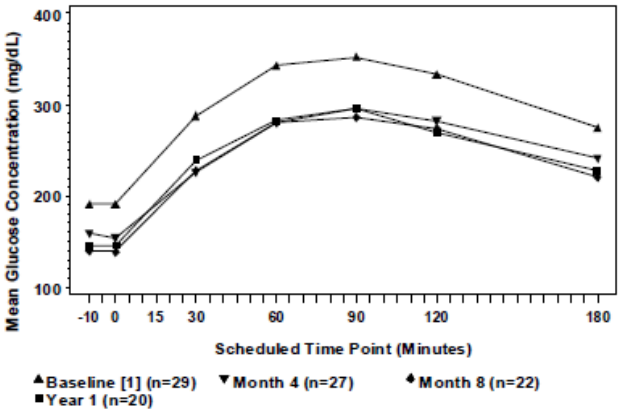
Oral Glucose Tolerance Test

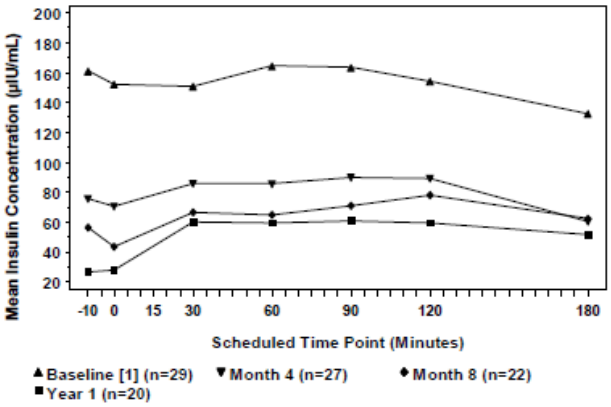
Mean plasma glucose and insulin profiles in response to an oral glucose tolerance test are presented in the figure below for the subpopulation from the 2005 data cut. At baseline, mean fasting plasma glucose values were elevated at close to 200 mg/dL with excursions to the mid-300s after the glucose load.

After four months of metreleptin treatment, both fasting glucose and the response to the glucose load were reduced, and improvements were sustained through Year 1. Corresponding changes from baseline in glucose AUC (0-3 hr) were (mean ± SE): -148.3 ± 49.4 mg*hr/dL at Month 4 and -158.8 ± 68.3 mg*hr/dL at Year 1.

Consistent with the improvement in glucose levels, the corresponding insulin profiles showed similar results, indicating improvement in insulin sensitivity. Corresponding changes from baseline in the insulin AUC (0-3 hr) in the oral glucose tolerance test were (mean ± SE): -234.0 ± 146.5 (µIU*hr/mL) at Month 4 and -408.3 ± 309.7 (µIU*hr/mL) at Year 1.

Figure 17. Mean Glucose and Insulin Profiles by Visit from the Oral Glucose Tolerance Test, 2005 Data Cut (N = 29)



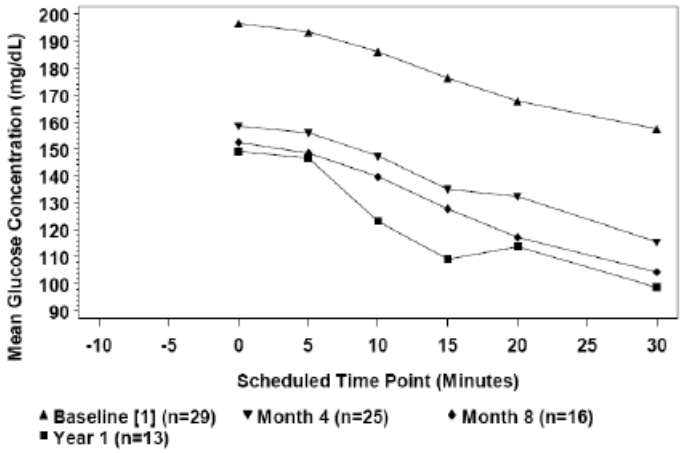


Notes: Baseline profile is defined as the last available profile before the patient received the first injection of metreleptin.
- Only the visits which are common to both cohort 1 and cohort 2 patients, and visits at which at least 12 patients had data were displayed.
- Time point 0 refers to the time when oral glucose solution was administered for the oral glucose tolerance test.
Source: NIH Study Report, Figure 10

Insulin Tolerance Test

Plasma glucose profiles in response to an insulin tolerance test (injection of 0.2 U insulin / kg body weight) are shown in the following figure for the subpopulation from the 2005 data cut. Similar to findings with the oral glucose tolerance test, the mean glucose profile in response to an intravenous insulin challenge was lower after Month 4 of metreleptin treatment, consistent with increased insulin sensitivity, with similar results observed at Month 8 and Year 1 of treatment.

Figure 18. Mean Glucose Profile by Visit from the Insulin Tolerance Test, 2005 Data Cut (N = 29)



Notes: Baseline profile is defined as the last available profile before the patient received the first injection of metreleptin.
- Only the visits which are common to both cohort 1 and cohort 2 patients, and visits at which at least 12 patients had data were displayed.
- Time point 0 refers to the time when regular human insulin was administered intravenously for insulin tolerance test.
Source: NIH Study Report, Figure 11

Resting Metabolic Rate and Body Composition

Resting energy expenditure was measured with indirect calorimetry and was decreased with metreleptin treatment by 134.4 ± 74.6 kcal/24 hr and 253.8 ± 122.3 kcal/24 hr (mean ± SE) at Month 4 (n=16) and Month 12 (n=16), respectively, from a baseline (n=22) of 1732.3 ± 77.9 kcal/24 hr.

Minimal or no changes in mean ± SE body fat as measured by skin fold thicknesses were observed with metreleptin treatment at Month 4 (+0.5 ± 0.7 %) and at Month 12 (+0.0 ± 0.6 %) from a baseline of 19.3 ± 1.4%.

Reviewer comment: The NIH published these data[19] and reported (using dual energy x-ray absorptiometry) that small decreases in fat mass and lean body mass, without change in bone mineral content or density, were seen after four months of metreleptin treatment but with no significant change from four to 12 months of continued treatment. The decrease in resting metabolic rate may reflect decreases in hyperphagia and energy intake.

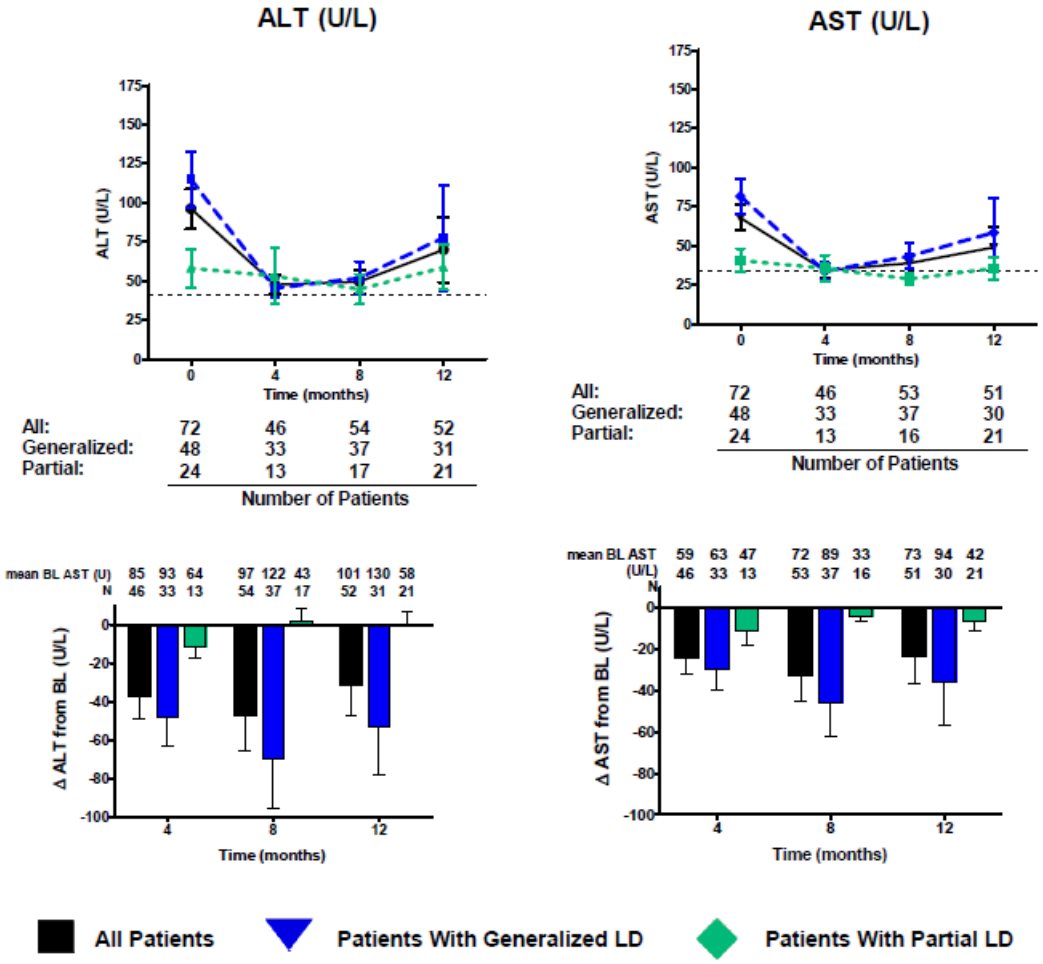
Hepatic Parameters

Given the propensity for patients with lipodystrophy to store fat ectopically, particularly in the liver, non-alcoholic fatty liver disease (NAFLD) is a commonly-described condition associated with this disease. When NAFLD is characterized as non-alcoholic

steatohepatitis (NASH), patients are at risk for developing hepatic fibrosis and cirrhosis, which can progress to liver failure. There are no currently FDA-approved drugs for the treatment of NASH.

The NIH study report included information on the effect on hepatic enzymes and liver volume, the FHA101 study report included limited information on hepatic enzyme changes, and the sponsor's clinical efficacy summary document included hepatic enzymes and liver volume. Limited pathology information (liver biopsies) were reported in two publications.[25,26] Our FDA colleagues in the Division of Gastroenetrology and Inborn Errors Products will be providing context and interpretation of these findings. Below is a summary of ALT and AST changes provided by the sponsor in the BLA.

Figure 19. Mean (SE) ALT and AST Concentrations Over Time and Change from Baseline at Month 4, 8, and 12: All Patients, Generalized Lipodystrophy and Partial Lipodystrophy (ITT Population Observed Data for Each Efficacy Parameter)



[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., ALT and AST) 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 the ULN for ALT (41 U/L) and AST (34 U/L).

Source: Clinical Efficacy Update, Figure 14

Endocrine Parameters

In females, improvements in LHRH-stimulated LH were noted after four months of metreleptin with increased estradiol and decreased testosterone levels. Results from the LHRH stimulation test are available prior to metreleptin in 17 female patients (limited data in one of these) and after four months of metreleptin treatment in 10 female

patients. LH levels increased approximately 4-fold from baseline to the peak value (60 min) in response to LHRH prior to metreleptin treatment. After four months of metreleptin, the LH peak induction was similar (approximately 4-fold) but longer lasting with the peak maintained from 60 to 180 min after LHRH.

Reproductive steroid hormone (serum estradiol and testosterone) levels were also measured at baseline and at 1, 4, 6, and 8 months after metreleptin treatment in patients from the NIH 991265 trial (all female). At baseline, mean ± SE estradiol concentrations were 37.1 ± 12.0 pg/mL, and mean total testosterone concentrations were 84.7 ± 31.4 ng/dL (n = 9). After four months of metreleptin treatment, estradiol increased to 72.5 ± 32.3 pg/mL and mean testosterone levels decreased to 33.6 ± 5.9 ng/dL (n = 8).

No changes in LHRH-stimulated LH occurred after metreleptin in the few males who had this test.

There was no effect of metreleptin treatment on the hypothalamic-pituitary-thyroid axis. Prior to metreleptin therapy, mean TSH increased in response to TRH from 1.6 ± 0.35 mIU/L at -15 min to a peak of 13.1 ± 2.0 mIU/L at 30 min (n = 12). After four months of metreleptin therapy, the TSH response to TRH showed similar results (from mean of 1.4 ± 0.37 mIU/L to a peak of 12.2 ± 1.9 mIU/L at 30 min, n = 8).

In addition, TSH, thyroxine (T4), and triiodothyronine (T3) levels were measured at baseline and during metreleptin treatment in patients from the NIH 991265 trial. Non-stimulated TSH concentrations in these patients were normal at baseline (1.2 ± 0.2 mIU/L, mean ± SE, [n = 9]) and remained stable through Month 4 (1.2 mIU/L ± 0.2, [n = 8]) and Month 8 (1.1 ± 0.2 mIU/L, [n = 8]). Mean (± SE) T3 concentrations (baseline: 115.2 ± 12.3 ng/dL, [n = 9]; Month 4: 111.0 ± 9.4 ng/dL [n = 8]; Month 8: 109.4 ± 10.2 ng/dL [n = 8]), and T4 concentrations (baseline: 10.5 ± 1.0 µg/dL [n = 6], Month 1: 11.3 ± 1.0 µg/dL [n = 4]) also remained stable.

There was no effect of metreleptin treatment on the hypothalamic-pituitary-adrenal axis. In patients from the NIH 991265 trial (n = 7), unstimulated ACTH and cortisol concentrations at baseline were 28.6 ± 4.8 pg/mL and 20.1 ± 4.3 µg/dL, respectively (mean ± SE). After four months of metreleptin treatment, mean ACTH and cortisol concentrations were largely unchanged (30.2 ± 4.6 pg/mL and 17.3 ± 2.2 µg/dL, respectively). In addition, the ACTH and cortisol response to CRH administration was similar before and four months after metreleptin therapy.

A diurnal ACTH and cortisol analysis was completed for patients enrolled directly into the NIH trial 20010769. Mean 8:00 am ACTH and cortisol levels at baseline were 39.1 ± 4.5 pg/mL (n = 13) and 21.8 ± 1.8 µg/dL (n = 19). After four months of metreleptin treatment, 8:00 am ACTH and cortisol levels were slightly lower but similar to baseline (33.9 ± 7.2 pg/mL and 15.3 ± 1.5 µg/dL, respectively, mean ± SE). At baseline,

midnight cortisol levels were low (5.8 ± 0.7 µg/dL, n = 19) as expected based on diurnal variation (and ruling out hypercortisolism) and did not change after four months of metreleptin (5.1 ± 1.1 µg/dL, n = 16).

6.1.6 Other Endpoints

See Section 6.1.5.

6.1.7 Subpopulations

Given the heterogeneity of lipodystrophy phenotypes, it is important to adequately characterize the effect of metreleptin in subpopulations, in order to identify patients who may or may not be likely to achieve benefit. As noted in the protocol description, the inclusion criteria for leptin concentrations at baseline in the NIH trial increased over time. Notably, patients enrolled in the initial trial had large improvements in metabolic endpoints,[22] whereas this effect appears less so in the subsequent trial enrollment. These earlier patients were primarily patients with generalized lipodystrophy, but patients with partial lipodystrophy were enrolled if they had low leptin concentrations.

Overall (and as would be expected), as shown in Table 34, patients with generalized lipodystrophy have a greater response in HbA1c and TG than patients with partial lipodystrophy and patients with lower baseline leptin concentrations have a greater response than patients with higher leptin concentrations.

Table 34. Change From Baseline to Month 12 in Key Efficacy Parameters: Intrinsic Factors (NIH; ITT Patients with Baseline and Month 12 Data)

	Mean (SE) HbA1c (%)			Mean (SE) FPG (mg/dL)			Median TG (mg/dL)			
Intrinsic Factor	N	BL	Δ from BL at Month 12	N	BL	Δ from BL at Month 12	N	BL	Δ from BL at Month 12	Percent Δ from BL at Month 12
Overall Population	50	8.2 (0.3)	-1.4 (0.2)	52	169.9 (12.3)	-41.8 (11.7)	51	359.0	-121.0	-44.8
LD Subtype										
CGL	20	9.0 (0.5)	-2.2 (0.4)	22	169.6 (16.3)	-32.3 (21.1)	22	452.0	-284.0	-60.7
AGL	9	8.0 (0.6)	-1.8 (0.4)	9	203.4 (38.2)	-87.6 (23.5)	8	348.0	-211.5	-67.4
FPL	17	7.7 (0.5)	-0.5 (0.3)	17	158.5 (22.8)	-32.5 (14.7)	17	357.0	-74.0	-29.8
APL	4	6.7 (1.4)	-0.1 (0.2)	4	144.3 (35.5)	-30.3 (52.8)	4	334.5	-50.5	-7.3
Gender										
Male	6	7.7 (1.0)	-1.3 (0.7)	7	135.4 (26.4)	-34.3 (18.7)	7	141.0	-40.0	-27.9
Female	44	8.3 (0.3)	-1.4 (0.2)	45	175.2 (13.5)	-42.9 (13.2)	44	427.0	-207.0	-49.6
Age										
≤12 yrs	11	6.1 (0.4)	-0.7 (0.4)	12	113.3 (13.9)	-25.0 (15.2)	12	230.0	-5.5	-5.2
>12 yrs to <18 yrs	14	9.8 (0.5)	-2.3 (0.4)	15	191.3 (26.8)	-35.9 (30.3)	15	433.0	-263.0	-66.1
<18 yrs	25	8.1 (0.5)	-1.6 (0.3)	27	156.7 (17.6)	-31.0 (17.9)	27	322.0	-115.0	-42.1
≥18 yrs	25	8.3 (0.4)	-1.2 (0.3)	25	184.2 (16.9)	-53.3 (14.7)	25	487.0	-300.5	-46.4
Race										
Caucasian	34	8.0 (0.4)	-1.1 (0.2)	35	171.3 (16.3)	-44.3 (12.5)	34	358.0	-110.0	-32.4
Hispanic	4	8.0 (1.5)	-2.4 (1.5)	4	173.3 (54.2)	-80.3 (51.5)	4	518.5	-393.0	-71.0
Black	5	8.4 (0.9)	-1.2 (0.9)	6	159.8 (28.6)	-1.8 (58.1)	6	679.5	-370.0	-47.3
Baseline Metabolic Abnormalities										
HbA1c ≥6%	40	8.9 (0.3)	-1.8 (0.2)	40	192.0 (13.8)	-52.3 (14.3)	39	433.0	-230.0	-54.2
Trig ≥200 mg/dL	36	8.4 (0.4)	-1.4 (0.3)	37	183.6 (15.6)	-45.9 (15.3)	37	503.0	-303.0	-54.2
HbA1c <6% and Trig <200 mg/dL	5	5.1 (0.2)	0.1 (0.2)	6	84.7 (4.8)	-2.2 (5.2)	6	129.5	13.0	10.7
Leptin Levels [1]										
Lower	36	8.3 (0.4)	-1.8 (0.3)	38	176.1 (15.1)	-49.7 (15.1)	38	424.5	-246.5	-55.2
Higher	12	7.7 (0.5)	-0.2 (0.2)	12	141.1 (20.6)	-21.0 (15.4)	12	298.0	-65.0	-24.4

[1] Lower: Male <2.0 ng/mL / Female <4.0 ng/mL; Higher: Male ≥2.0 ng/mL / Female ≥4.0 ng/mL.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 23

Reviewer comment: Note that baseline HbA1c and fasting TG values for AGL and FPL are similar, yet patients with AGL seem to have had a better response than patients with FPL. In addition, baseline TG was similar for APL, AGL, and FPL, yet patients with APL had less TG-lowering.

The following table and figures illustrate the differences in metabolic improvements over time by lipodystrophy type (generalized or partial) overall and in those patients with various degrees of baseline abnormalities.

Table 35. Key Efficacy Parameters at Baseline and Month 12 in Generalized and Partial Lipodystrophy: All Patients and Patients with Elevated HbA1c, Fasting Glucose, and TG, NIH Trials

HbA1c (%)	All			Baseline HbA1c ≥6%			Baseline HbA1c ≥7%			Baseline HbA1c ≥8%		
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized LD	29	8.7 (0.4)	-2.0 (0.3)	26	9.1 (0.3)	-2.3 (0.3)	24	9.3 (0.3)	-2.4 (0.3)	19	9.8 (0.3)	-2.7 (0.3)
Partial LD	21	7.5 (0.5)	-0.4 (0.2)	14	8.6 (0.5)	-0.8 (0.3)	11	9.2 (0.5)	-1.0 (0.4)	7	10.1 (0.6)	-1.4 (0.4)
Fasting Glucose (mg/dL)	**All**			**Baseline Glucose ≥126 mg/dL**								
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12						
Generalized LD	31	179.5 (15.9)	-48.3 (16.9)	21	218.6 (17.8)	-82.1 (16.5)						
Partial LD	21	155.8 (19.3)	-32.1 (14.8)	11	220.9 (22.5)	-68.6 (23.2)						
Fasting TG (mg/dL)	**All**			**Baseline TG ≥200 mg/dL**			**Baseline TG ≥350 mg/dL**			**Baseline TG ≥500 mg/dL**		
Median	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized LD	30	414.5	-246.5	21	600.0	-432.0	17	836.0	-692.0	12	1526.5	-1117.0
Partial LD	21	357.0	-74.0	16	430.0	-95.5	11	550.0	-298.0	7	1237.0	-499.0

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.
In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin.

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 3

Reviewer comment: Changes in efficacy parameters are shown in a number of analyses by higher baseline value cutoffs, including the table above (e.g., baseline HbA1c 8% or greater). These data should be interpreted with caution; without a comparator group, the potential for contribution of a regression to the mean the the proported greater improvements in these subgroups cannot be dismissed.

The following table summarizes additional endpoints in patients with generalized versus partial lipodystrophy in the NIH trials.

Table 36. Change From Baseline in Efficacy Parameters for Patients with Generalized and Partial Lipodystrophy, NIH Trials

	Generalized lipodystrophy (N=48)			Partial lipodystrophy (N=24)		
	Month 4	Month 8	Month 12	Month 4	Month 8	Month 12
FFA (mEq/L)	n=24 -249.88	n=24 -199.88	n=22 -158.41	n=11 -596.09	n=15 -322.53	n=14 -401.50
Total cholesterol	n=33 -73.82	n=36 -61.08	n=31 -95.23	n=13 -62.23	n=17 -72.12	n=21 -27.14
LDL-C (mg/dL)	n=24 -21.58	n=26 -31.27	n=21 -34.33	n=6 -0.33	n=7 -6.86	n=11 -14.73
HDL-C (mg/dL)	n=32 -0.63	n=35 -0.34	n=31 -1.10	n=12 -2.58	n=15 0.13	n=19 -0.11
ALT (U/L)	n=33 -47.82	n=37 -69.84	n=31 -52.84	n=13 -11.23	n=17 1.76	n=21 0.29
AST (U/L)	n=33 -29.67	n=37 -45.51	n=30 -35.70	n=13 -11.08	n=16 -2.50	n=21 -6.62
Liver volume (mL)	n=19 -662.76	n=18 -948.58	n=11 -1454.18	n=4 -253.00	n=6 -200.17	n=6 -171.33

Source: Summary of Clinical Efficacy, Supporting Data Summaries 2.16.4 and 2.16.7

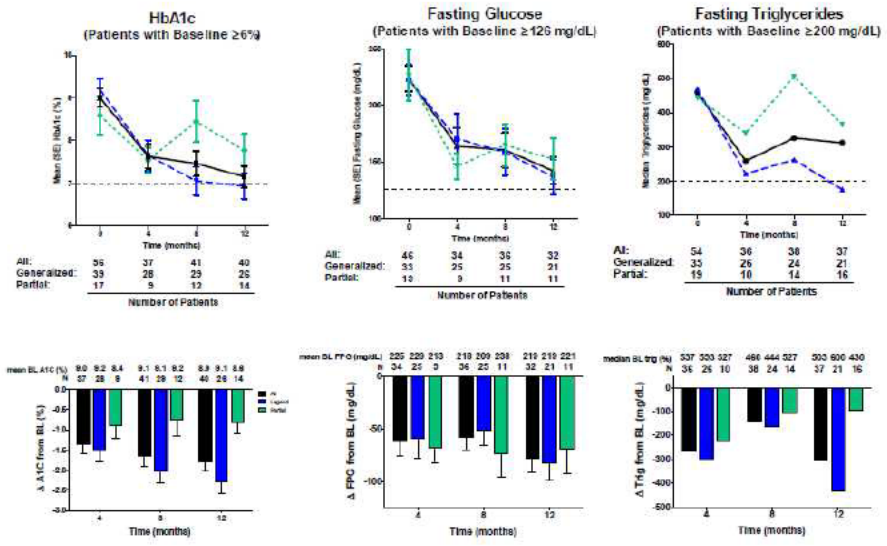
Table 37. Key Efficacy Parameters at Baseline and Month 12 in Generalized and Partial Lipodystrophy: All Patients and Patients with Elevated HbA1c, FPG, and TG, FHA101

HbA1c (%)	All			Baseline HbA1c ≥ 6%			Baseline HbA1c ≥ 7%		
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized	2	7.3 (1.8)	-1.1 (0.3)	1	9.1 (na)	-1.3 (na)	1	9.1 (na)	-1.3 (na)
Partial	8	8.7 (0.6)	-0.9 (0.6)	8	8.7 (0.6)	-0.9 (0.6)	7	9.0 (0.6)	-1.0 (0.7)
Fasting Glucose (mg/dL)	**All**			**Baseline Glucose ≥ 126 mg/dL**					
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12			
Generalized	2	186.0 (76.0)	-81.0 (48.0)	1	262.0 (na)	-129.0 (na)			
Partial	8	172.9 (17.5)	-42.0 (22.4)	7	184.4 (15.2)	-49.7 (24.2)			
Fasting TG (mg/dL)	**All**			**Baseline TG ≥ 200 mg/dL**			**Baseline TG ≥ 500 mg/dL**		
Median	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized	2	5488.5	-5403.5	2	5488.5	-5403.5	1	10623.0	-10483.0
Partial	8	322.5	-81.0	5	341.0	-166.0	1	919.0	-644.0

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 4

Reviewer comment: Although the FHA101 trial (Table 37) does not appear to demonstrate the same degree of discrepancy in HbA1c change between generalized and partial lipodystrophy patients as the NIH trials (see Table 35, above), note that in FHA101 the mean baseline HbA1c in the two patients with generalized lipodystrophy who have 12 month data is lower than that of the patients with partial lipodystrophy. Contrast the baseline HbA1c values in FHA101 to those in the NIH trials (i.e., the mean value in the generalized patients in the NIH trials was similar to the mean value in the partial patients in the FHA101 trial and vice versa). This supports the concept that the observed greater improvements in HbA1c in the generalized patients may be partially independent of baseline values. (Although the small sample sizes, lack of a placebo control, and changes in concomitant medications limit the conclusions.) Results in generalized and partial lipodystrophy, overall and by baseline metabolic abnormalities are further explored in figures and tables below.

Figure 20. Key Efficacy Parameters in Patients with Baseline HbA1c 6% or Greater, FPG 126 mg/dL or Greater, or TG 200 mg/dL or Greater: All Patients, Generalized Lipodystrophy, and Partial Lipodystrophy (NIH; Observed Data for Each Efficacy Parameter)



[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.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 2

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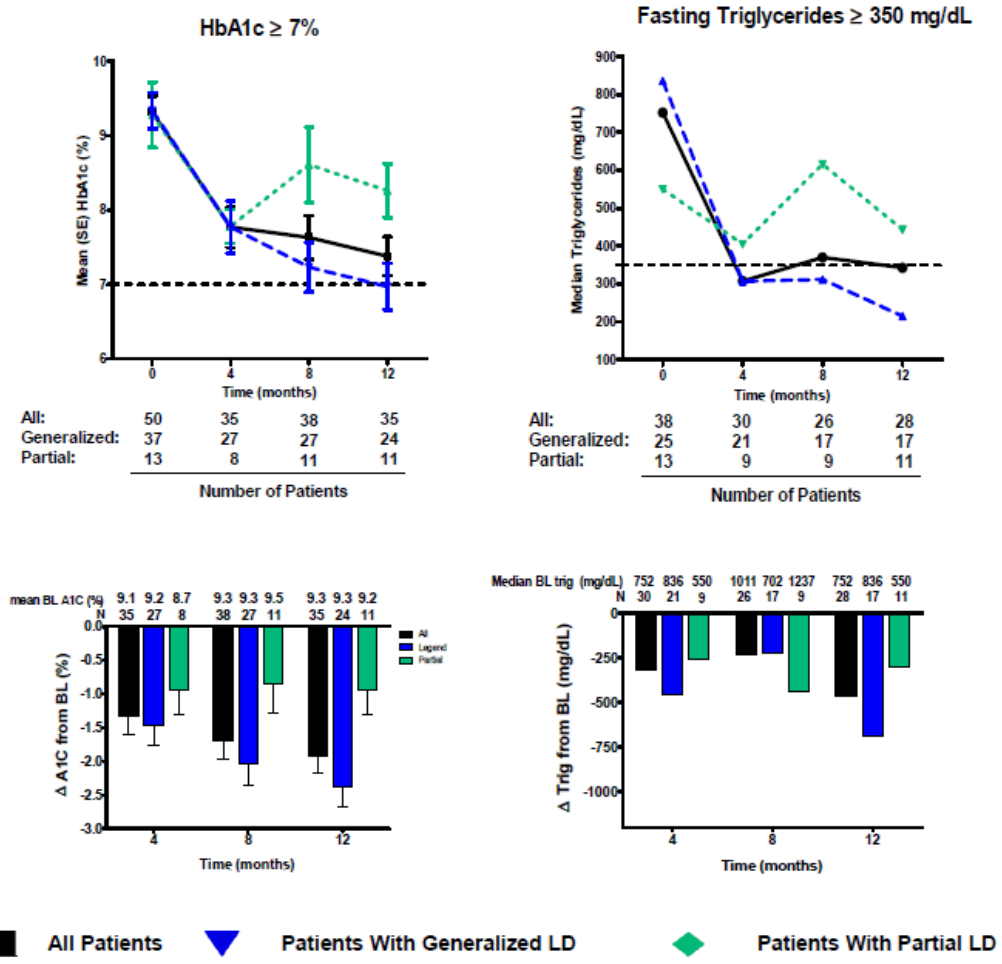
Figure 21. Key Efficacy Parameters in Patients with Baseline HbA1c 7% or Greater, or TG 350 mg/dL or Greater: All Patients, Generalized Lipodystrophy, and Partial Lipodystrophy (NIH; Observed Data for Each Efficacy Parameter [1])



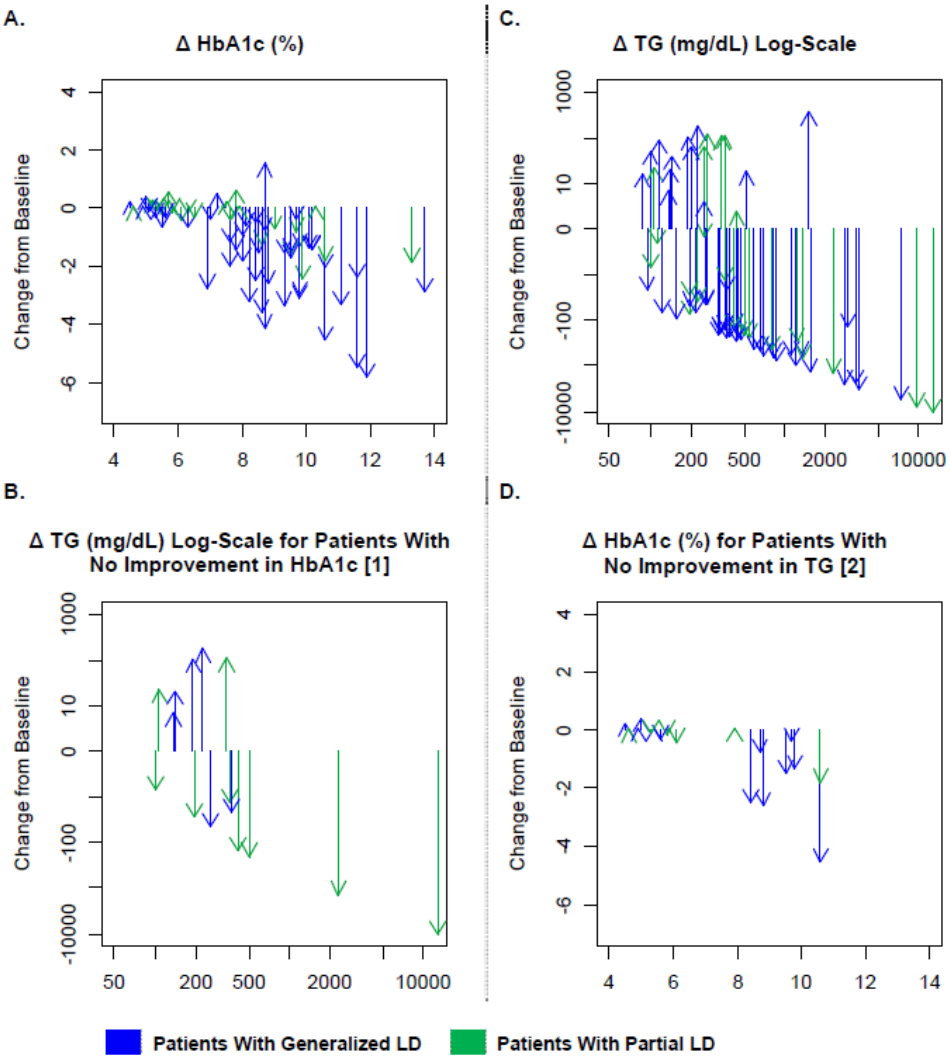
[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time 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.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 3

Reviewer comment: These figures further support metreleptin benefit for patients with generalized lipodystrophy who have significant metabolic complications (notwithstanding the reviewer's comment about baseline abnormalities, above). Even in the subgroup with elevated HbA1c and TG at baseline, patients with partial lipodystrophy appear to have attenuated responses as compared with generalized patients.

Figure 22 demonstrates the relationship between the severity of baseline metabolic abnormalities (HbA1c and TG) and changes in these parameters over time.

Figure 22. Average Change from Baseline in HbA1c and Fasting TG during the First 12 Months of Metreleptin Treatment versus Baseline Value for Individual Patients: Generalized and Partial Lipodystrophy, NIH Trials



[1] No improvement is defined as patients with ≥0% increase in HbA1c.
[2] No improvement is defined as patients with ≥0 mg/dL increase in TG.

Note: The x-axis represents the baseline value
Source: Clinical Efficacy Update, Figure 4

Reviewer note: In Chart B, the patient with the largest downward arrow is presumed to be Patient 90152 (30 yo F FPL), whose Baseline TG was 12697 mg/dL and Month 8 TG was 2320 mg/dL. At Month 18, the patient's TG was 7557 mg/dL, reflecting the variability of TG over time.

Reviewer comments: Note that while most patients have a favorable (or unchanged) HbA1c response, the TG response is more variable. This may be that TG is influenced by factors other than insulin resistance (e.g., short-term changes in dietary composition, genetic factors, etc.). This suggests that while TG improvements in patients with lipodystrophy treated with metreleptin may be due to improvements in insulin resistance, to the extent that patients also have hypertriglyceridemia for other reasons (potentially related to the type of lipodystrophy), metreleptin's effects may be more variable. As noted previously, without a placebo control it is challenging to interpret some of these findings and accurately estimate the treatment effect.

A review of patients who only have uncontrolled severe hypertriglyceridemia (TG 500 mg/dL or greater) without uncontrolled diabetes (HbA1c 7 mg/dL or greater), suggested that (1) this is an uncommon finding (4%), and (2) in the case of two of the three patients with partial lipodystrophy, improvements in TG were confounded by concomitant medication changes. The one-year-old patient with CGL (90168) who had improvements in TG only, not HbA1c, clearly had severe insulin resistance at baseline, with a fasting insulin concentration of 303 µU/mL (not shown in the table below).

Table 38. Triglyceride Values Over Time and Relevant Concomitant Medications for Patients Enrolling with only Severe Hypertriglyceridemia Without Associated Uncontrolled Diabetes Mellitus

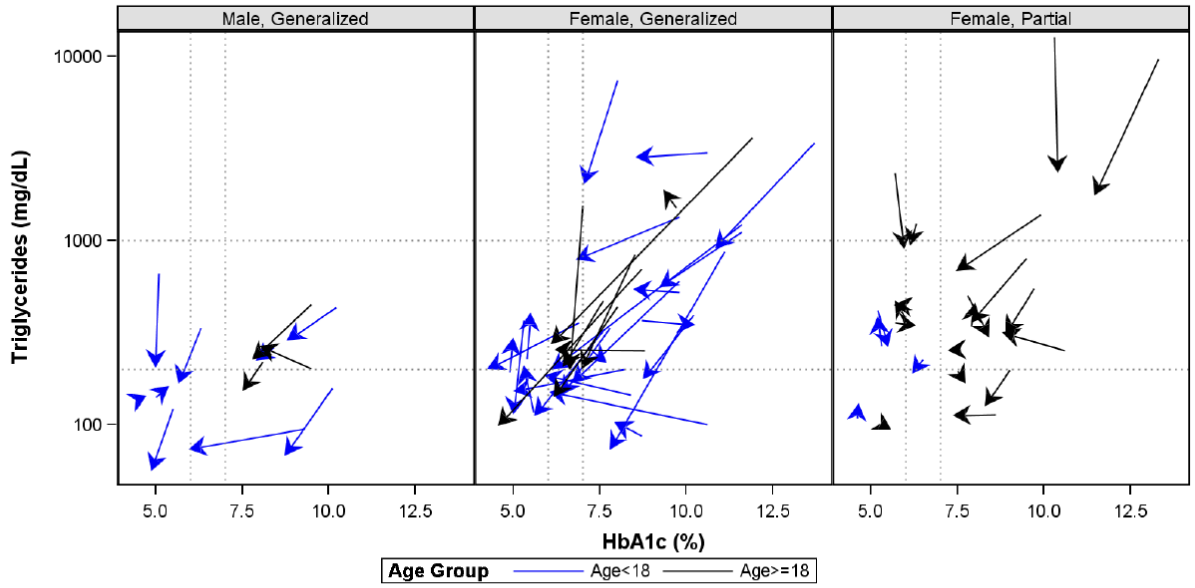
Patient ID / Demog / BL HbA1c	NIH: Study day (Visit) FHA101: Visit (description)	TG (mg/dL)	Medication comments
NIH Patient 90121 / 32 yo F FPL / 5.7%	-4 (Baseline)	2324	Atorvastatin at baseline
	122		Started fish oil, fenofibrate
	132 (Month 4)	530	
	286 (Month 8)	752	
	412 (Month 12)	1825	
	571 (Month 18)	7010	
NIH Patient 90132 / 18 yo F APL / 6.3%	-7 (Baseline)	1237	
	112 (Month 4)	1048	
	240 (Month 8)	1578	
	357		Started fenofibrate
	365 (Month 12)	494	
NIH Patient 90168 / 1 yo M CGL / 5.1%	-1 (Baseline)	663	
	87 (Month 4)	204	
FHA101 Patient 648018 / 40 yo F APL / 5.7%	Visit 1 (Day 1)	1243	Fish oil at baseline
	Visit 5 (Month 3)	436	
	Visit 6 (Month 6)	399	
	Visit 7 (Month 9)	471	

Source: Reviewer generated from BLA 125390 datasets: DLABS, DLABS 2, DCLINLAB

The following figures are provided as additional summaries of the relationship between HbA1c and TG changes in the NIH trials.

In Figure 23, each patient is represented by a vector, whose start represents the baseline HbA1c (horizontal axis) and TG (vertical axis) value, and whose pointed end represents the average of that patient's post-baseline values through Month 12 for HbA1c (arithmetic mean) and TG (geometric mean). Thus, vectors that point from right to left indicate a reduction in HbA1c at Month 12, vectors that point downward reflect improvement in TG concentrations, and vectors pointing diagonally downward and to the left represent improvement in both HbA1c and TG. Vectors are presented for patients who had HbA1c and TG data available for baseline as well as at least one post-baseline value. Furthermore, this plot includes color coding to indicate pediatric (less than 18 years) versus adult (18 years or older) patients.

Figure 23. Change From Baseline to Average Post-Baseline Values of HbA1c and Geometric Mean of Post-Baseline Values of TG Up to 12 Months for Individual Patients by Sex and Generalized versus Partial Lipodystrophy (NIH Trials)

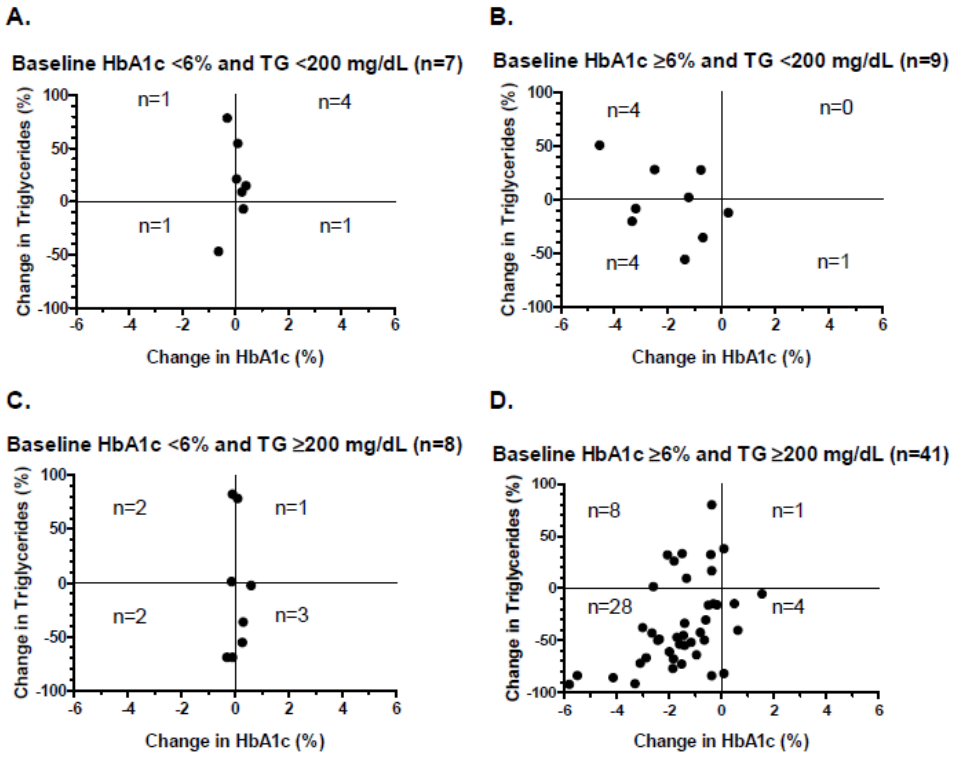


[1] Horizontal Axes: HbA1c values. Vertical Axes: Triglyceride values. Arrows begin at the BL value (A1c or TG) and end with post baseline value (pointed end of arrow.)
Length of Arrow: Magnitude of change from baseline with upward arrow (increase from baseline) and downward arrow (decrease from baseline).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

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 10

Figure 24 provides an alternative view of the above figure, with the percent change in TG plotted against the change in HbA1c (average of the first 12 months of treatment) for each patient with at least one post-baseline value during the initial 12 months of metreleptin treatment, according to the baseline metabolic status.

Figure 24. Change From Baseline to Average Post-Baseline Values of HbA1c and Percent Reduction in TG Up to 12 Months for Individual Patients by Baseline Metabolic Abnormality Category (NIH; Patients with Baseline and at Least One Post-Baseline Measurement)



Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 6

An exploration was done of factors that might predict which individual patients within subpopulations respond beneficially to metreleptin. As demonstrated above, patients with generalized lipodystrophy, particularly those with uncontrolled metabolic disease appear to have the most robust response. Baseline fasting leptin could also be an important factor; particularly given the observation that patients in earlier versions of the NIH protocol utilized lower fasting leptin values as a key eligibility criterion. Over the entire cohort, patients with generalized lipodystrophy had mean fasting leptin (SD) of 1.3 ng/mL (1.1) and those with partial lipodystrophy had a value of 4.9 ng/mL (3.1).

The relationship between baseline leptin and response to metreleptin treatment was specifically evaluated in patients with partial lipodystrophy who had a wider range of baseline leptin values compared with patients with generalized lipodystrophy who were almost all “low” leptin (i.e., less than 2 ng/mL, males; less than 4 ng/mL, females). All three endpoints (HBA1c, FPG, and TG) demonstrated greater change from baseline for patients with lower baseline leptin concentration in patients with partial lipodystrophy.

Table 39. Change From Baseline to Month 12 in Key Efficacy Parameters by Leptin Level Categories, NIH Trials

	Mean (SE) HbA1c (%)			Mean (SE) FPG (mg/dL)			Median TG (mg/dL)			
Leptin Level Category (ng/mL)	N	BL [3]	Δ from BL at Mo. 12	N	BL [3]	Δ from BL at Mo 12	N	BL [3]	Δ from BL at Mo. 12	% Δ from BL at Mo.12
GENERALIZED										
All										
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	26	8.6 (0.4)	-2.1 (0.3)	28	175.5 (17.3)	-47.6 (18.4)	28	415	-247	-64
Min, Max		4.9, 13.7	-5.8, 0.7		71, 478	-232, 271		87, 7420	-5977, 473	-93, 90
≥4 (Female) / ≥2 (Male)										
Mean (SE) /Median [1]	1	10.1 (na)	-1.6 (na)	1	200.0 (na)	-134.0 (na)	1	158.0	-105.0	-66.5
Min, Max		na	na		na	na		na	na	na
Elevated Baseline	**Baseline HbA1c ≥ 6%**			**Baseline FPG ≥ 126 mg/dL**			**Baseline TG ≥ 200 mg/dL**			
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	23	9.1 (0.4)	-2.4 (0.3)	18	219.1 (20.4)	-86.7 (18.2)	20	562	-395	-74
Min, Max		6.3, 13.7	-5.8, 0.7		126, 478	-232, 74		261, 7420	-5977, 473	-93, 90
≥4 (Female) / ≥2 (Male)										
Mean (SE) /Median [1]	1	10.1 (na)	-1.6 (na)	1	200.0 (na)	-134.0 (na)	-	-	-	-
Min, Max		na	na		na	na		-	-	-
PARTIAL [2]										
All										
<4 (Female)										
Mean (SE) /Median [1]	10	7.6 (0.9)	-0.9 (0.4)	10	177.8 (32.5)	-55.5 (26.7)	10	609	-237	-29
Min, Max		4.6, 13.3	-3.1, 0.6		65, 367	-224, 17		108, 9702	-8866, 521	-91, 194
≥4 (Female)										
Mean (SE) /Median [1]	11	7.5 (0.5)	-0.1 (0.2)	11	135.7 (21.8)	-10.7 (12.5)	11	343	-64	-18
Min, Max		5.3, 10.6	-0.7, 0.9		49, 284	-88, 48		101, 550	-298, 115	-54, 40
Elevated Baseline	**Baseline HbA1c ≥ 6%**			**Baseline FPG ≥ 126 mg/dL**			**Baseline TG ≥ 200 mg/dL**			
<4 (Female)										
Mean (SE) /Median [1]	6	9.2 (1.0)	-1.6 (0.4)	6	239.0 (35.6)	-99.2 (34.4)	8	1020	-429	-37
Min, Max		6.3, 13.3	-3.1, -0.3		151, 367	-224, -28		255, 9702	-8866, 521	-91, 194
≥4 (Female)										
Mean (SE) /Median [1]	8	8.1 (0.5)	-0.2 (0.2)	5	199.2 (25.7)	-31.8 (23.9)	8	358.0	-65	-16
Min, Max		6.1, 10.6	-0.7, 0.9		145, 284	-88, 48		227, 550	-298, 115	-54, 40

[1] Data represent Mean (SE) for HbA1c and FPG; Median for TG;
[2] All patients with partial LD in NIH were females.

[3] For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and Month 12.

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 5

Table 40. Change From Baseline to Month 12 in Key Efficacy Parameters by Leptin Level Categories, FHA101 Partial Lipodystrophy Patients††††††

	HbA1c (%)			FPG (mg/dL)			TG (mg/dL)			
Leptin Level Category (ng/mL)	N	BL [2]	% Δ from BL at Mo. 12	N	BL [2]	% Δ from BL at Mo. 12	N	BL [2]	Δ from BL at Month 12	% Δ from BL at Mo. 12
PARTIAL										
All										
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	1	11.1 (na)	-4.7 (na)	1	242.0 (na)	-127.0 (na)	1	193	-101	-52
Min, Max		na	na		na	na		na	na	
≥4 (Female) / ≥2 (Male)										
Mean (SE) / Median [1]	7	8.3 (0.6)	-0.3 (0.3)	7	163.0 (16.7)	-29.9 (21.7)	7	341	-61	-18
Min, Max		6.5, 11.0	-2.0, 0.4		92, 211	-114, 43		66, 919	-644, 129	-70, 39
Elevated Baseline	**Baseline HbA1c ≥6%**			**Baseline FPG ≥126 mg/dL**			**Baseline TG ≥ 200 mg/dL**			
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	1	11.1 (na)	-4.7 (na)	1	242.0 (na)	-127.0 (na)	-	-	-	-
Min, Max		na	na		na	na	-	-	-	-
≥4 (Female) / ≥2 (Male)										
Mean (SE) / Median [1]	7	8.3 (0.6)	-0.3 (0.3)	6	174.8 (14.0)	-36.8 (24.3)	5	341	-166	-47
Min, Max		6.5, 11.0	-2.0, 0.4		130, 211	-114, 43		304, 919	-644, 129	-70, 38

[1] Data represent Mean (SE) for HbA1c and FPG; Median for TG.
[2] For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and Month 12.

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 7

By Age

The pediatric population (N = 39) in the NIH trials changed over time, as the age criterion was lowered as the protocol progressed. The pediatric population was predominantly female (77%) and white (54%). Of the 39 pediatric patients, 35 (90%) were diagnosed with generalized lipodystrophy (26 congenital and nine acquired), and four patients (10%) were diagnosed with partial lipodystrophy (two familial and two acquired). The mean age of the pediatric population at baseline was 12 years (range: one to 17 years), with 17 (44%) 12 years old or younger and 22 (56%) older than 12 to younger than 18 years old.

While baseline HbA1c abnormalities were comparable in pediatric and adult patients (8.1% pediatric, 8.4% adult), there was a greater percentage of pediatric patients with HbA1c less than 6% (n = 11, 28%) versus adults (n = 4, 12%).

Baseline TG levels were higher in adult versus pediatric patients (mean TG 1346 mg/dL versus 791 mg/dL), although this was driven by two adult patients having TG values greater than 9000 mg/dL. The median TG in adult patients was 446.5 mg/dL versus 335.0 mg/dL in pediatric patients

The percentage of pediatric patients with TG less than 200 mg/dL was higher compared to adults (n = 13, 33% and n = 4, 12%, respectively). (Of note, 95 percent of children and adolescents 12 to 19 years old in the general United States population have a TG

†††††† Results in the 5 patients in FHA101 with generalized lipodystrophy are presented separately in Table 29; all patients (with leptin concentrations available) were in the "low" leptin category.

concentration between 61-88 mg/dL; in children and adolescents with obesity 6 to 19 years old, the TG range is from 79-94 mg/dL.[27])

Of seven patients with baseline HbA1c less than 6% and TG less than 200 mg/dL (enrolled on the basis of insulin resistance), six (15%) were pediatric compared to one (3%) adult. However, these pediatric patients were more likely to have liver findings reported at baseline. A greater percentage of pediatric patients (67- 80%) had elevated liver enzymes compared to adult patients (42- 46%), and mean AST and ALT were higher in pediatric compared to adult patients. Per the NIH investigator, patients enrolled in the study based on insulin resistance were generally enrolled only if they also had evidence of clinically significant liver disease related to lipodystrophy (hepatic steatosis / steatohepatitis).

See Table 34 and Figure 23 for a summary of results by age groups.

Reviewer comment: The subgroup results presented in Table 34 suggest that children less than 12 years of age may receive less benefit from metreleptin than other age groups. However, there were some young children who did appear to respond to treatment. The likely reason that the young children subgroup (i.e., less than 12 years of age) did not demonstrate robust mean changes was that this group was less likely to have significant abnormalities in baseline HbA1c and TG.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

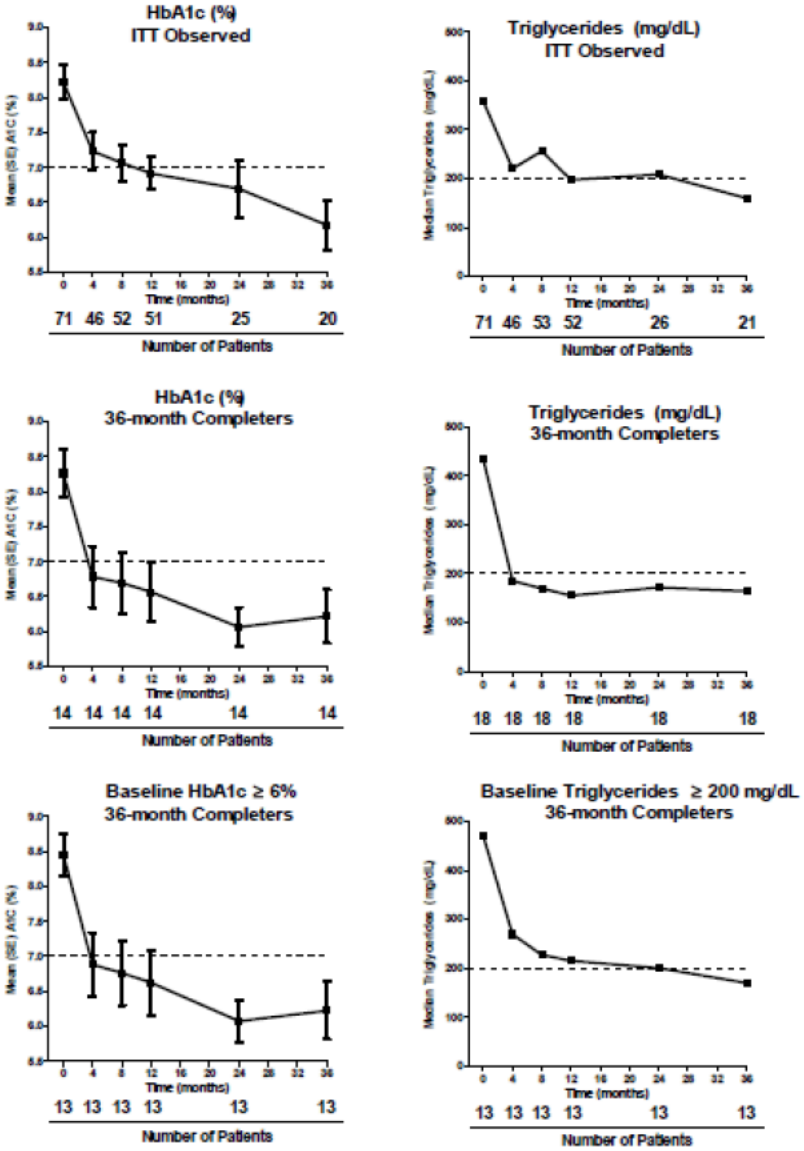
The proposed dosing recommendations in the label were based on the dosing regimen that the NIH investigators used and became comfortable with over time[‡‡‡‡‡‡] and were ultimately adopted by the treatment protocol (FHA101).

[‡‡‡‡‡‡] The following comment in the NIH protocol regarding dose adjustments was noted (emphasis added):
In individuals above the age of 5 years, the dose of metreleptin will be increased beyond 0.12 mg/kg/day only if there is a clear decline in metabolic status without alternative explanations for the metabolic change (such as an infection, noncompliance, or dietary indiscretion). ***It is important to note this because of the wide range of variation in the clinical presentation of these patients it is impossible to define pre-determined thresholds of metabolic parameters that would appropriately guide dose modifications. Instead, the PI will use best clinical judgment to make dose modifications based on the constellation of metabolic and clinical data available to each patient.*** *The dose of metreleptin can be increased from 0.08 mg/kg/day after the 4-month follow-up. All dose escalations will be performed in increments of 0.02 mg/kg/day for females 10 years of age and older, and 0.015 mg/kg/day in all other study participants. Only one dose increase may be done per week, in order to evaluate the effect on body weight and on injection sites. Dose escalation will be capped such that the total dose administered will not exceed 0.24 mg/kg/day for any patient without seeking prior permission from the FDA, the IRB, and Amylin, Inc., the manufacturer of metreleptin. If subjects do not tolerate a higher dose level, they can continue the study at the next lowest tolerated dose.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Although some patients were exposed to metreleptin for years, it is notable that many patients prematurely discontinued from the trial and/or were non-compliant. Therefore, efficacy in patients treated for the long-term could be confounded by relevant patient characteristics (e.g., willing to return for visits, highly motivated, highly compliant, etc.). Nevertheless, longer-term data are available. The evaluation of greater duration of treatment has to be balanced against the diminishing numbers of patients with data at later time points; therefore, the sponsor chose a 36-month time point as a reasonable balance of these factors to assess durability of effect. The following figures present HbA1c and TG over 36 months in all patients available (ITT), “completers” (i.e., patients who were available at all time points), and patients with elevated baseline HbA1c and TG values.

Figure 25. Mean (SE) HbA1c and Median TG from Baseline to Month 36 (NIH; Observed, 36 Month Completers, and 36 Month Completers with Baseline HbA1c 6% or Greater and TG 200 mg/dL or Greater)



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[1] Dashed lines denote common treatment goals and/or diagnostic criteria for HbA1c of 7%; TG of 200 mg/dL.
[2] 36-month completers are defined as receiving at least 36 months of metreleptin treatment and having data for the specified efficacy measure at baseline, M4, M8, M12, M24, and M36.

Source: Clinical Efficacy Update, Figure 11

Reviewer comment: Note that 36-month completers for HbA1c and TG only make up 19% and 25%, respectively, of the total population. Therefore, it is unknown how representative these results are of the lipodystrophy population overall.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Patients with lipodystrophy can present with significant co-morbidities, often as a result of the complications of lipodystrophy (e.g., pancreatitis, atherosclerosis, cirrhosis), or reflecting an underlying autoimmune disease as in the case of many patients with acquired lipodystrophies. It is particularly challenging to assess the safety of metreleptin and adjudicate its role in a variety of adverse events, given the high background incidence of co-morbid disease and the theoretical possibility that metreleptin may exacerbate certain conditions via its activation of the Janus kinase signal transducer and activator of transcription (JAK-STAT) and other intracellular pathways, as well as its effects on the immune system. Safety issues of particular interest in this development program include the following:

- T-cell lymphoma: Three cases of T-cell lymphoma have been reported in patients with AGL in the NIH trials. Two of the cases occurred in patients with hematological disease (neutropenia, lymphadenopathy) at baseline and were on confounding medications, such as G-CSF and erythropoietin. A third patient (13-year-old with AGL) did not have any known hematological disorders or other confounding factors prior to developing lymphoma, aside from the AGL diagnosis. Leptin is a cytokine that exerts its effect by binding to the leptin receptor on cell surfaces and activating the JAK-STAT intracellular pathway. Leptin signaling via JAK-STAT and other pathways promotes cell growth and survival and inhibits apoptosis. Dysregulation of STAT proteins and signalling contributes to the pathogenesis of some malignancies. It is unknown if metreleptin could promote the progression of lymphoma or other malignancies in a patient population that is predisposed to these diseases. Of note, hematological malignancies, including T-cell lymphoma, have been reported in the literature in patients with lipodystrophy not treated with metreleptin.

- Immunogenicity: Metreleptin is highly immunogenic. The majority of patients exposed in clinical trials developed anti-leptin antibodies. Development of binding antibodies is associated with supraphysiological concentrations of circulating leptin, as well as inflammatory injection site adverse events. To some extent, the long-term clinical sequelae of antibody development are unknown. Nevertheless, a number of adverse events associated with the development of antibodies with neutralizing activity, particularly in patients treated with metreleptin in the development program for obesity (not currently active), has highlighted a potential risk for off-label use. Three patients in the obesity program have been identified with the development of neutralizing antibodies. All three patients presented with high antibody titer, low

leptin concentrations, and excessive body weight gain (13 kg to 66 kg above baseline body weight). One patient in the lipodystrophy program was recently identified as having developed high-potency, highly reproducible, neutralizing anti-leptin antibodies. This patient, a 19-year-old female with CGL, appears to have had some loss of efficacy (HbA1c) based on the last measured efficacy parameters and, perhaps more significantly, has had five hospitalizations as a result of various bacterial infections over this past summer. Because of the role that leptin plays in the functioning of the immune system, it is theoretically possible that neutralizing antibodies to leptin could have implications for immune functioning (i.e., immunodeficiency), even in patients with very low endogenous leptin. An additional unanswered question related to the development of neutralizing antibodies in the lipodystrophy population is whether a risk of maternal-fetal transfer of neutralizing antibodies exists, and whether a baby born to a mother with neutralizing antibodies could develop a congenital leptin deficiency-like condition.

- Autoimmunity: Leptin activates a number of cell signaling pathways important in T-cell activity and is permissive in cellular proliferation and cytokine production. Therefore, exacerbation of autoimmunity is a theoretical concern, given leptin's role in the immune system. In the NIH trials, adverse events of autoimmune hepatitis and membranoproliferative glomerulonephritis (associated with massive proteinuria and renal failure) exacerbations were seen in some patients with AGL treated with metreleptin. The contribution of metreleptin in these cases is unknown, but appears plausible.

- Other Immune-Related Adverse Events: Other potentially immune-related adverse events in the lipodystrophy trials included urticaria, pruritus, arthralgia, asthma, rash, and facial swelling. (A single anaphylactic reaction was thought likely food-related.) In a summary of five pooled placebo-controlled obesity trials, severe injection site reactions were reported in 0.9% of metreleptin-treated patients versus 0.3% of placebo-treated patients. Other injection-site adverse events occurring more frequently in metreleptin-treated compared to placebo-treated patients included injection site erythema (10.8% versus 0.6%), injection site inflammation (4.8% versus 0.6%), injection site edema (2.3% versus 0.0%), injection site pruritus (8.0% versus 1.7%), and injection site rash (2.4% versus 0.0%). In the pooled obesity trials, non-injection site reaction adverse events reported as associated with hypersensitivity were experienced by 14% of metreleptin-treated patients versus 8% of placebo-treated patients. A serious adverse event of systemic hypersensitivity occurred in an obesity trial participant.

- Hypoglycemia: Hypoglycemia was the most frequent adverse event reported in the lipodystrophy trials. In the NIH trials, hypoglycemia was reported only in those patients receiving concomitant insulin therapy with or without oral anti-hyperglycemic agents. No severe hypoglycemia events (e.g., requiring the assistance of another individual) were reported. In FHA101, one patient experienced a severe event of

hypoglycemia that required assistance from another person. In this trial, most events of hypoglycemia occurred in patients who were receiving concomitant insulin therapy or a sulfonylurea with or without other oral antihyperglycemic agents, except one patient who experienced an event of hypoglycemia while on metformin only. In patients with type 2 diabetes mellitus in the pooled obesity trials, 14.3% of patients on metreleptin and 5.0% of patients on placebo reported hypoglycemia.

- Pancreatitis: Patients with lipodystrophy are predisposed to acute pancreatitis, due to marked hypertriglyceridemia (often defined as TG greater than 1000 mg/dL). In the NIH trials, 16 (22.2%) patients had a medical history of pancreatitis and 4 (5.6%) patients had a history of recurrent pancreatitis. Although some patients treated with metreleptin appeared to have significant improvement in TG concentrations, many patients continued to have high or fluctuating TGs, and adverse events of pancreatitis were seen in the lipodystrophy trials. As there was no control group, and the trials were not powered to detect either an improvement or worsening in pancreatitis, the potential contribution of metreleptin on pancreatitis events in a patient population predisposed to this adverse event is unknown. The sponsor has proposed that patients who developed pancreatitis in the lipodystrophy program were non-compliant or they discontinued or interrupted metreleptin too rapidly with subsequent rebound in serum TG. Of note, in the pooled obesity trials, one patient treated with metreleptin (out of 784) had a serious adverse event of pancreatitis, versus no placebo-treated patients (out of 351).

- Liver-Related Adverse Events: Patients with lipodystrophy who have undergone liver biopsy have been described to fall within the spectrum of non-alcoholic fatty liver disease (NAFLD), from none to inflammation and fibrosis (including cirrhosis), as well as having other liver diseases such as autoimmune hepatitis. Seven patients in the lipodystrophy development program had adverse events related to the liver; all had liver-related abnormalities at baseline. Notably, five out of the seven events occurred in patients with AGL, three of whom had known autoimmune hepatitis at baseline. No patient in the lipodystrophy program met the laboratory criteria for Hy's law (i.e., ALT or AST greater than 3x ULN accompanied by total bilirubin greater than 2x ULN); however, a patient in the NIH trial (18-year-old female with AGL) with a history of cirrhosis died due to progressive end-stage liver disease.

- Nephropathy: Proteinuric nephropathies have been associated with lipodystrophy, and approximately one third of the patients in the lipodystrophy program had a medical history of proteinuria. In the NIH trials, worsening of renal disease (proteinuria or creatinine increases or adverse events relevant to proteinuric nephropathies) was seen in 12 patients, and five of those patients were known to have ultimately progressed to end-stage renal disease, despite transient improvements in proteinuria in some cases. The contribution of metreleptin to the worsening of underlying renal disease is unknown; however, an effect on autoimmune-related renal disease in patients with AGL appears plausible.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following table is similar to the table presented in Section 5.1 (Table 6), with the exception of descriptions of additional investigational trials that have been conducted with metreleptin in a variety of patient populations. Where available, the safety data from these trials are presented in this section.

Table 41. Studies Supporting the Metreleptin for Lipodystrophy BLA and Other Studies and Compassionate Use Treatment Involving Metreleptin Administration

Study	Patient Population	Number of Metreleptin-Treated Patients	Position in BLA	Endpoints Supported
NIH Trials 991265/20010769 [1]	Lipodystrophy patients	72 [2]	Pivotal	Safety and efficacy
Treatment IND FHA101 [1]	Lipodystrophy patients	28 [3]	Supporting	Safety and efficacy
Amgen 5-trial ISS (metreleptin monotherapy)	Obese patients without lipodystrophy	784	Supporting	Safety (including immunogenicity)
10 other Amgen obesity trials (metreleptin monotherapy)	Obese patients without lipodystrophy	379 [4]	Supporting	Immunogenicity
Amylin obesity program (metreleptin/pramlintide combination)	Obese patients without lipodystrophy	615	Supporting	Immunogenicity
Other investigator-initiated trials [1]	Lipodystrophy patients Rabson-Mendenhall	92 [5]	[7]	[7]
Compassionate use treatment [1]	Lipodystrophy patients	51 [5][6]	[7]	[7]
Compassionate use treatment [1]	Congenital leptin deficient patients	18 [5]	[7]	[7]
Other investigator-initiated trials in other indications	HIV-associated lipodystrophy, obesity, NASH, HA, type 1 DM, healthy subjects	248	[7]	[7]

NASH=non-alcoholic steatohepatitis; HA=hypothalamic amenorrhea; DM=diabetes mellitus
[1] ongoing trials or ongoing treatment, except investigator-initiated study with C. Levy Marchal as principal investigator
[2] As of 11 July 2011 data cut
[3] As of 7 Mar 2012 data cut
[4] Excludes 4 patients with congenital leptin deficiency treated with metreleptin in Amgen trial 970161
[5] As of January 2013
[6] Excludes patients who initiated metreleptin treatment though other trials (e.g., NIH trials, other investigator-initiated trials)
[7] Note that although these trials were not included in the BLA, in response to an FDA information request the sponsor provided some limited safety information; see Section 7.7, Additional Submissions / Safety Issues; individual adverse events were also presented in some other sections of the safety review

Source: BLA 125390, Section 2.5 Clinical Overview, date 27 Mar 2013; sponsor response to FDA 24 Jun 2013, Table 3

A total of 13 clinical studies were conducted by Amgen under IND 50,259 to support the development of metreleptin for the treatment of obesity. Amgen, who was at the time of the initial proposal for the BLA, the sponsor of these data, selected five of these trials to form the basis of the supporting ("supplemental") integrated summary of safety (ISS). Criteria for inclusion into this supplemental ISS include: Phase 2, randomized, placebo-controlled trials of metreleptin administered by subcutaneous injection to overweight/obese individuals (with or without type 2 diabetes) with treatment duration of at least 12 weeks. The obesity development program was terminated prior to initiation of any Phase 3 studies.

The five studies that met these criteria were:

- LEPT-970164, LEPT-970213, and LEPT-980236, which were conducted in overweight/obese patients without type 2 diabetes; and

- LEPT-970171 and LEPT-970188 conducted in overweight/obese patients with type 2 diabetes.

Among these, LEPT-980236 was designed as a 52-week trial, with a planned sample size of 340 patients randomized to treatment. Although this trial was terminated early due to the sponsor's discontinuation of the metreleptin for obesity development program, and none of the randomized patients completed the study, it was included in the ISS because most (67%) of the 267 patients randomized to treatment completed 12 weeks of treatment and 44% completed 24 weeks of treatment.

Reviewer comment: FDA and the sponsor agreed that data from these five obesity trials could be pooled to support the safety assessment (see Table 4). There are limitations to the pooling approach, including the variable trial durations, the premature discontinuation of the 52-week trial, and a trial design (a different trial) that included an induction period in which all patients were treated with metreleptin prior to randomization (decribed in Section 7.3.2, Nonfatal Serious Adverse Events). The advantages to the pooling are that there are a relatively large number of patients, and there is a placebo control.

Additional trials evaluated for certain safety issues (i.e., deaths, nonfatal serious adverse events, and adverse events of special interest) include Amgen trials evaluating metreleptin for obesity that were not included in the ISS, and trials from the Amylin metreleptin-pramlintide combination development program for obesity. These trials are listed below.

Table 42. Summary of Studies from the Amylin Metreleptin + Pramlintide Program (DFA) and the Amgen Metreleptin Trials not Included in the Five-Trial ISS

Study	Design	Patient Population	Number Treated With Metreleptin
DFA102/102E	Phase 2, randomized, double-blind, placebo-controlled, 28-week dose-ranging study with an open-label extension up to 52 weeks	Obese without LD	496 [1]
DFA103	Phase 1, open-label, cross-over bioavailability study	Obese and overweight without LD	78
DFA104	Phase 2B, randomized, double-blind, placebo-controlled, study to examine the efficacy and safety following a low-calorie diet lead-in	Obese without LD	36
Amgen Studies			
LEPT-950272	Randomized, double-blind, placebo-controlled, 24-week dose-ascending study	Non obese and obese without LD	177
LEPT-960176	Follow-up open-label, 24-month study	Obese without LD	151
LEPT-960240	Randomized, double-blind, placebo-controlled, CSCI, individual ascending-dose, 30-week study	Obese without LD	23
LEPT-970161	Open-label dose-ascending study	Obese with congenital leptin deficiency (due to leptin gene mutation)	4
LEPT-970121	Randomized, double-blind, placebo-controlled, IV, dose- ascending, 30-day study	Healthy	83
LEPT-970211	Randomized, double-blind, placebo-controlled, 16-week dose-ascending study	Obese without LD	5
LEPT-980219	Randomized, double-blind, placebo-controlled, 24-week study	Non-obese and obese without LD, with type 2 diabetes treated with Met or Met in combination with a SU	44
LEPT-980145	Randomized, double-blind, placebo-controlled, 24-week dose-ascending study	Overweight and obese without LD, with type 2 diabetes	6 (A-100)
LEPT-980225	Randomized, double-blind, placebo-controlled, 24-week study	Overweight without LD, with type 2 diabetes treated with insulin alone or insulin in	18
LEPT-980298	Phase 1, PK comparison and safety study	Obese without LD	24 (A100/300)[2]
		Total Treated with Metreleptin	1228

Met=metreleptin; pram=pramlintide; LD=lipodystrophy; SU=sulfonylurea, Met=metformin, CSCI=continuous subcutaneous infusion, IV=intravenous, PK=pharmacokinetic
[1] DFA102E is an extension study of DFA102 with 273 subjects enrolled in the extension.

[2] A-100 is Amgen's designation for metreleptin and A-300 is an analog of A-100 with a sequence modification to improve solubility under physiological condition.

Source: Response to FDA Request for Information Dated 24-May-2013; Question 1, Table 1-1

7.1.2 Categorization of Adverse Events

Although the sponsor utilized MedDRA[28] to categorize adverse events, because of the relatively small size of the database, many adverse events are presented in list form and are counted according to clinical scenarios (e.g., pancreatitis, potentially immune-related, etc).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The lipodystrophy trials are presented for safety as they were for efficacy: adverse events, laboratory data, and vital signs are tabulated for the NIH trials and FHA101 trial.

In the ISS (five Amgen obesity trials), all patients who received at least one injection of randomized study medication (metreleptin or placebo) were included in the analyses. An exception is for LEPT-970213 in which eligible participants were randomized into the treatment period (Part C) after a three-week dietary lead-in period (Part A) and a four-week metreleptin 10 mg BID induction period (Part B). All 228 participants who received at least one dose of metreleptin during the metreleptin induction period (Part B) were included and counted as metreleptin-treated. Among these 228 patients, 189 patients (126 to metreleptin and 63 to placebo) were randomized into the 24-week treatment period (Part C). The 63 patients who were randomized to placebo treatment in the 24-week treatment period (Part C) were counted as both metreleptin-treated (induction period) and placebo-treated (randomized treatment period), and the analyses were conducted as appropriate depending on the period when data were collected.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 43. Number of Patients in Completed and Ongoing Studies Who Received at Least One Dose of Metreleptin as of the Original BLA Cutoffs and the Clinical Safety Update Cutoffs

Trial	Original BLA	Clinical Safety Update
NIH		
N	55	72
Data Cutoff Date	31 July 2009	11 July 2011
FHA101		
N	10	28
Data Cutoff Date	14 June 2010	07 March 2012
Total	65	100

Source: BLA 125390 Clinical Safety Update, 27 March 2013 Submission, Table 1

The data cutoffs for the FHA101 trial were more recent compared to the NIH trial due to the reported logistical issues associated with performing a data cut for an investigator-sponsored clinical study versus the Amylin-sponsored FHA101. In addition, patients in FHA101 generally returned every three months for follow-up visits whereas study visits were more infrequent in the NIH study due to travel considerations for the majority of the patients.

Integrated safety results from five Phase 2, randomized, placebo-controlled trials of metreleptin administered by subcutaneous injection in 1072 overweight and obese patients (784 exposed to metreleptin) with or without type 2 diabetes with treatment duration of at least 12 weeks, with a range of exposure from one day up to 42 weeks, provide supplemental safety data for metreleptin use in humans. A total of 162 patients were exposed to metreleptin for more than 24 weeks.

7.2.2 Explorations for Dose Response

For the 72 patients treated with metreleptin in the NIH pivotal studies, the starting total daily dose ranged from 0.4 mg to 15 mg. Because of the dose titration specified by protocol and subsequent dose adjustments based on individual clinical response, as well as evolution of the dosing regimen over time, a weighted average dose that accounted for the duration of time at a specific dose was calculated as:

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

Weighted average daily doses used up to one year, weighted average daily doses used over the entire study period, and maximum doses used over the study period are summarized in both mg/kg as well as total mg in the following table.

- Mean weighted average daily dose over the entire study period was 6.1 mg (range 0.8 to 19.1 mg) for females and was 2.9 mg (range 0.9 to 6.9 mg) for males.

- Mean weighted average dose up to one year was lower than that over the entire study period and is most likely attributed to lower starting doses followed by dose titration during the initial months of metreleptin treatment.

- As of the 11 Jul 2011 data cutoff, the maximum daily dose of metreleptin administered to any patient ranged from 0.9 mg to 20 mg (0.9 to 20 mg females; 0.9 mg to 10 mg males), with most patients (58 of 72) receiving 10 mg/day or less.

Table 44. Total Daily Doses of Metreleptin by Sex and Generalized versus Partial Lipodystrophy, NIH Trials

		Daily Dose in mg/kg			Daily Dose in mg		
Gender, Diagnosis		Weighted Average up to 1 Year [1]	Weighted Average Over Study Period [2]	Maximum Over Study Period	Weighted Average up to 1 Year [1]	Weighted Average Over Study Period [2]	Maximum Over Study Period
Male, Generalized LD							
(N = 12)	Mean (SE)	0.046 (0.004)	0.053 (0.006)	0.07 (0.01)	2.37 (0.23)	2.93 (0.43)	3.95 (0.66)
	Min, Max	0.03, 0.08	0.03, 0.10	0.04, 0.14	0.9, 4.3	0.9, 6.9	0.9, 10.0
	CV %	33.64	37.49	43.90	32.91	50.95	57.43
Female, Generalized LD							
(N = 36)	Mean (SE)	0.077 (0.005)	0.099 (0.006)	0.12 (0.01)	4.08 (0.49)	5.29 (0.57)	6.57 (0.75)
	Min, Max	0.02, 0.21	0.02, 0.21	0.03, 0.26	0.8, 18.7	0.8, 19.1	0.9, 20.0
	CV %	41.32	36.28	44.94	71.45	64.27	68.74
Female, Partial LD							
(N = 24)	Mean (SE)	0.092 (0.005)	0.117 (0.007)	0.15 (0.01)	5.71 (0.50)	7.27 (0.58)	9.19 (0.86)
	Min, Max	0.06, 0.18	0.07, 0.20	0.08, 0.25	1.0, 11.1	1.0, 13.2	1.2, 20.0
	CV %	27.96	27.69	34.89	43.10	38.75	46.00
All Female Patients							
(N = 60)	Mean (SE)	0.083 (0.004)	0.107 (0.005)	0.13 (0.01)	4.73 (0.37)	6.09 (0.43)	7.62 (0.59)
	Min, Max	0.02, 0.21	0.02, 0.21	0.03, 0.26	0.8, 18.7	0.8, 19.1	0.9, 20.0
	CV %	36.40	33.31	41.18	59.96	54.30	59.79

[1] Average up to one year is weighted by time for each patient according to the formula: Sum[Daily Dose*Duration (Days) of the Dose Regimen]/Total Days of All Dose Regimens, restricted to the first year of dosing.
[2] Average over the entire study period is weighted by time for each patient according to the formula: Sum[Daily Dose*Duration (Days) of the Dose Regimen]/Total Days of All Dose Regimens, over the study period.

Source: Clinical Efficacy Update, Table 7

7.2.3 Special Animal and/or In Vitro Testing

In vitro testing was conducted to assess the neutralizing activity of anti-drug antibodies. The assessment of the adequacy of this evaluation is pending review from the Office of Biotechnology Products.

7.2.4 Routine Clinical Testing

Limitations to assessing the adequacy of routine clinical testing were addressed in Section 3.1, Submission Quality and Integrity. In addition, there were significant limitations to the antibody assessment as discussed in Section 7.4.6, Immunogenicity.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal metabolic, clearance, or interaction assessments were conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

Patients Treated for Lipodystrophy

In a published case series of 70 patients with CGL, eight (11%) patients died prematurely between the ages of 19 months and 35 years.[29] It is also notable that deaths in two patients with CGL were reported while awaiting metreleptin treatment in the NIH protocol (one who died at age 30 of sudden cardiac death and another age 31 who died of idiopathic pulmonary fibrosis).[30]

In the NIH trials, as of the 11 July 2011 cutoff, three deaths were reported out of 72 ITT patients: one patient out of 55 in the 31 July 2009 cutoff and two patients between the 2009 and the 2011 cutoffs.

In addition, in the NIH trials, two deaths (31 July 2009 cutoff) occurred several months after discontinuation of metreleptin treatment.

In the FHA101 trial, as of the 07 March 2012 cutoff, two adverse events leading to death were reported out of 28 ITT patients: one patient in the 14 June 2010 cutoff and one patient between the 2010 and 2012 cutoffs.

In the four-month safety update in which an additional 25 patients were enrolled from the previous data cutoffs to the new data cutoff of January 2013 (total N = 125) there was one additional report of death from a patient in the NIH trials (no additional deaths in the FHA101 trial).

Therefore, a total of eight (6.4%) patients enrolled in the lipodystrophy trials up until the January 2013 data cutoff died (N=125);[§§§§§§] six (4.8%) of these patients were on metreleptin therapy or within one month of drug discontinuation at the time of death.

Narratives for these six patients are as follows [discussions of the two deaths that occurred more than one month after discontinuation of metreleptin are discussed with: (1) the serious adverse events in Section 7.3.2 (Patient 90109 hypoalbuminemia, worsening of proteinuria, and worsening of liver disease); and (2) the discussion of malignancies in Section 7.6.1 (Patient 90147 T-cell lymphoma)[§§§§§§]]:

- Renal failure (NIH Trial): At study entry, Patient 90106 was a 35-year-old black female with CGL. Other relevant past medical history at study entry included pneumonia, hyperlipidemia, diabetes, peripheral vascular disease, proteinuria, total knee replacement, hip replacement, a history of smoking, avascular necrosis, and left shoulder pain. The patient experienced a serious adverse event of myoclonus, muscular weakness, and pain in extremity on Day 2 (09 Sep 2000) of metreleptin treatment and a serious adverse event of respiratory distress on Day 13 (20 Sep 2000) of metreleptin treatment. She was treated with metreleptin from 15 Nov 2000 until 16 Jan 2002 when she stopped study medication on 16 Jan 2002 and discontinued study participation. On 29 Aug 2008 (approximately six and half years after discontinuing study participation), the patient resumed study participation at the NIH and restarted metreleptin treatment. She had one follow-up visit at the NIH in May 2009, which was her last visit there. At that time, it was noted that her kidney disease, originally noted in 2000 prior to ever starting study medication, had worsened, as evidenced by her decreasing creatinine clearance. The patient stated she did not desire dialysis and expressed reservation about nephrology follow-up as she did not want dialysis. On (b) (6), the patient's brother called the NIH to report that the patient had died on (b) (6) (approximately one and a half years after restarting metreleptin treatment) from kidney failure. The brother reported that the patient was not feeling well on (b) (6) and went to the local emergency room seeking care. The patient was sent home, but returned (b) (6) as she still was not feeling well. She went into cardiac arrest, and was unable to be resuscitated. The emergency room physician told the family the patient was in kidney failure, went into shock, and was unable to be resuscitated. She received the last dose of study medication on 03 Mar 2010.

[§§§§§§] An additional patient was known to have died 8 months after study discontinuation (Patient 90115, T-cell lymphoma); but this death was not captured in the total because the event leading to death was not reported as an adverse event.

Reviewer comment: It is unclear what the precipitating event was for this patient's death. It is noted that she was sent home from the Emergency Department the day prior to cardiac arrest from reported renal failure.

- Progressive end-stage liver disease (NIH Trial): At study entry, Patient 90158 was an 18-year-old Hispanic female patient with AGL. Relevant past medical history at study entry included severe liver disease with cirrhosis, elevated ammonia levels, constipation, hypercholesterolemia, mild renal insufficiency, proteinuria, diabetes, and pancytopenia. On (b) (6), on Day 346 of treatment with metreleptin, the patient experienced a serious adverse event of hepatic encephalopathy with altered consciousness related to constipation and taking pain medications for the constipation. The event resolved within a few days after receiving lactulose, and she was discharged in good condition. On (b) (6), the NIH was informed that the patient had been in the hospital for a few weeks due to chronic hepatic failure and was placed on life support and died on (b) (6). The final dose of study medication was administered that day. The patient had received approximately 1.4 years of metreleptin treatment at the time of her death. No further information is available.

Reviewer comment: It is not clear if the patient's liver disease was due to non-alcoholic steatohepatitis (NASH) or if she had autoimmune hepatitis (or both). It appears that some patients with AGL also have autoimmune hepatitis. In theory, metreleptin could make an autoimmune disease such as autoimmune hepatitis worse, even if there is an improvement in NASH. However, this is speculative in this case.

- Pancreatitis, septic shock, and cardiac arrest (NIH Trial): At study entry, patient 90125 was a 15-year-old Native American female with CGL. Other relevant past medical history at study entry included history of pancreatitis (further details not available), hypertension, diabetes, focal segmental glomerulosclerosis, and hyperlipidemia (TG 1669 mg/dL at baseline visit 22 Sep 2003). On (b) (6), Day 104 of treatment with metreleptin, the patient was hospitalized with pancreatitis. The patient was diagnosed with a ruptured pseudocyst of the pancreas and subsequently developed septic shock leading to cardiac arrest. The patient was resuscitated and an emergency laparotomy was performed in an attempt to locate a possible ruptured pseudocyst of the pancreas; this was not found. The patient subsequently died on (b) (6) when life support was removed in the absence of brain activity. The patient took metreleptin up to (b) (6) (the day prior to admission for pancreatitis). The investigator noted that according to the patient's local physician, she only took metreleptin 4 to 5 times per week although she should have been taking it 14 times per week. No follow-up study assessments on metreleptin were performed in this patient. It was the investigator's opinion that the

pancreatitis occurred because the patient was not compliant with metreleptin and that the metreleptin should have been tapered.

Reviewer comment: It is unclear what the diagnosis of ruptured pseudocyst was based on, considering that a laparotomy was apparently unrevealing.

- Progressive adenocarcinoma (FHA101 Trial): At study entry, patient 649001 was a 67-year-old white female with AGL. Relevant medical history included adenocarcinoma of undetermined origin, ascites, and esophageal reflux.******* On (b) (6) (b) (6), approximately 79 days after starting treatment with metreleptin, the patient experienced emesis, with blood noted, and an acute exacerbation of abdominal pain. It was unclear if the patient had a previous history of abdominal pain, but had been taking Zantac as needed for symptoms of reflux. Her metreleptin was temporarily stopped on (b) (6). The patient was admitted to the hospital and underwent an abdominal computerized tomography scan on (b) (6) which revealed rounded calcified deposits in the pelvis and faint calcifications over the liver dome, likely from mucinous adenocarcinoma metastases, mild hypertrophy of the left liver lobe, and bilateral pleural effusions. An upper gastrointestinal endoscopy was performed on (b) (6), which was consistent with severe erosive esophagitis. A small bowel series performed on (b) (6) demonstrated subjectively delayed gastric emptying. On the same day, the patient underwent paracentesis, at which time 3200 mL of amber fluid was removed. The patient was treated with intravenous Nexium and Zofran. She was started on total parenteral nutrition (TPN) and had a peripherally inserted central catheter placed. The patient was discharged home on (b) (6), and the event of erosive esophagitis was considered by the investigator as resolved on that day. Additional information was received from the investigator on 27 Sep 2010, which indicated that the events of the prior hospitalization were consistent with progressive adenocarcinoma of undetermined origin (onset date of (b) (6)), complicated by a small bowel obstruction. The patient had a Do Not Resuscitate order and she died on (b) (6) (b) (6). She had not resumed metreleptin treatment after stopping on (b) (6).

Reviewer comment: Because this patient was enrolled in the simplified protocol in the FHA101 trial, not much information was provided about this patient's medical history or condition at the start of the trial (i.e., it was not reported whether her illness was presumed to be terminal at the time she was enrolled in the trial). This appears to be a fairly rapid progression of her disease. It is unknown if metreleptin could have contributed to the worsening of the adenocarcinoma (i.e, as a tumor promotor).

******* Additional relevant past medical history that apparently was not captured in the database but reported in the Clinical Safety Update included cutaneous T-cell lymphoma (mycosis fungoides) diagnosed in 1981 that resolved with natural therapies. Note that because this patient was enrolled in a simplified protocol, information regarding medical history was not provided in the case report form.

- Loss of consciousness (FHA101 Trial): At study entry, patient 648008 was a 67-year-old white female with APL. Relevant medical history at study entry included diabetes since age 10, gastroparesis, high triglycerides since age 10, high cholesterol, hypertension, fatty liver, increased LFTs, coronary artery disease, s/p two cardiac stents in 2006, peripheral vascular disease, s/p axillofemoral bypass in 2006, autoimmune overlap syndrome (rheumatoid arthritis and systemic lupus erythematosis), autoimmune retinitis, hypothyroidism, anxiety, seizures in 2009, and history of smoking (one pack per day for more than 30 years). On (b) (6), day 51 of treatment with metreleptin, the patient tripped and fell in her home. She was known to have hit her head in the fall and was seen by her primary care physician and was deemed to be alright. The patient had three uneventful days. On (b) (6) (b) (6), she complained of fatigue and was noted to have a cough (which had begun approximately three weeks prior). On (b) (6), day 56 of treatment with metreleptin, the patient told her son that she felt hot, skipped dinner, and went to bed at approximately 6 pm. At 10 pm, the patient awoke, used the restroom and when she came out experienced weakness, confusion, and became unresponsive and lost consciousness. Her son noted that she seemed to be having a seizure. She was resuscitated by EMS after approximately 10-20 minutes. Evaluation in the ICU over the next several days suggested that her prognosis for neurologic recovery was very poor. A CT of the head (b) (6) revealed acute bilateral tentorial subdural hematoma. The decision to discontinue invasive supportive care was made and the patient died on (b) (6). No autopsy was conducted.

- Anoxic encephalopathy (NIH Trial): At study entry (16 Dec 2008), patient 90151 was a 27-year-old white female with a history of FPL. Relevant past medical history at study entry included type 2 diabetes mellitus, hypertriglyceridemia, hypertension, atrial septal defect, non-alcoholic steatohepatitis, recurrent pancreatitis, acute renal failure, asthma, sleep apnea, gastroparesis, gastroesophageal reflux disease, chronic cholecystitis, neuropathy, depression, insomnia, obsessive-compulsive disorder, tobacco use, and multiple allergies (codeine, morphine, oxycodone, sulfamethoxazole and latex). Recent serious adverse events prior to this event included severe abdominal pain in July 2011, lower gastrointestinal hemorrhage in October 2011, and ovarian dermoid cyst in November 2011. On (b) (6), after approximately 3.4 years of treatment with metreleptin, the patient's mother found her unconscious in her apartment. The patient was admitted to the Intensive Care Unit of a local hospital and diagnosed with anoxic encephalopathy. Metreleptin therapy was interrupted upon admission (last dose on (b) (6)). The patient never regained consciousness, and died on (b) (6) under hospice care. The death certificate listed the cause of death as anoxic encephalopathy, with diabetes mellitus, hypertension, and Dunnigan-Kobberling syndrome as underlying conditions leading to death, and chronic pancreatitis, sleep apnea and seizures as other significant conditions contributing to death. Tobacco use was also listed as probably contributing to death. Per the site, seizures reported on the death certificate most

likely occurred during the patient's hospitalization. No further information was provided. An autopsy was not performed.

The following table lists the eight deaths in the lipodystrophy trials, including the two patients (90109, 90147) who died after trial discontinuation. §§§§§§

Table 45. Deaths in the Lipodystrophy Trials: NIH and FHA101

Trial	Cutoff date	Patient	Age / sex / lipodystrophy type	Past medical history	Cause of death	Duration of metreleptin therapy
NIH	31 Jul 2009	90125	15 yo / F / CGL	Pancreatitis, hypertension, diabetes, focal segmental glomerulosclerosis, and hyperlipidemia (BL TG 1669 mg/dL)	Pancreatitis, subsequent septic shock leading to cardiac arrest	104 days
NIH	31 Jul 2009	90147	59 yo / F / AGL	Severe neutropenia, abnormal bone marrow, lipoatrophic diabetes, history of benign breast fibroma, non-alcoholic steatohepatitis	Multisystem organ failure related to peripheral T-cell lymphoma	242 days
NIH	31 Jul 2009	90109	13 yo / F / AGL	Steatohepatitis with bridging f brosis, membranoproliferative glomerulonephritis	Hepatorenal failure	444 days
NIH	11 Jul 2011	90106	35 yo / F / CGL	Pneumonia, hyperlipidemia, diabetes, peripheral vascular disease, proteinuria, total knee replacement, hip replacement, history of smoking, avascular necrosis, and left shoulder pain	Renal failure leading to cardiac arrest	428 days (first treatment) 554 days (second treatment)
NIH	11 Jul 2011	90158	18 yo / F / AGL	Severe liver disease with cirrhosis, elevated ammonia levels, constipation, hypercholesterolemia, mild renal insufficiency, proteinuria, diabetes, and pancytopenia	Chronic hepatic failure leading to death	526 days
NIH	After 11 Jul 2011	90151	27 yo / F / FPL	Chronic cholecystitis, type 2 diabetes, hepatosteatosis, hypertriglyceridemia, hypertension, atrial septal defect, depression, sleep apnea, gastroparesis, gastroesophageal reflux disease, insomnia, recurrent pancreatitis, obsessive compulsive disorder, tobacco user, and multiple allergies†††††††	Anoxic encephalopathy (found unconscious)	1232 days
FHA101	14 Jun 2010	648008	67 yo / F / APL	Diabetes, gastroparesis, hypertriglyceridemia, high cholesterol, hypertension, fatty liver, increased LFTs, coronary artery disease s/p 2 cardiac stents, peripheral vascular disease s/p axillofemoral bypass, autoimmune overlap syndrome, autoimmune retinitis, hypothyroidism, anxiety, seizures, history of smoking	Loss of consciousness	56 days
FHA101	07 Mar 2012	649001	67 yo / F / AGL	Adenocarcinoma of undetermined origin, ascites, and esophageal reflux	Progressive adenocarcinoma	79 days

Source: BLA 125390, Clinical Safety Update (27 Mar 2013 submission); NIH adverse event listings; FHA101 adverse event listings; Summary of Clinical Safety

††††††† The case report form also reported past medical history of motor and sensory neuropathy, diabetic retinopathy, asthma, and acute renal failure

Patients Treated for Obesity

In the five Amgen obesity trials (LEPT-970164, LEPT-970213, LEPT-980236, LEPT-970188, and LEPT-970171) summarized in the integrated summary of safety (ISS), 1072 obese patients received at least one dose of randomized study medication (metreleptin or placebo). Of these patients, 784 received metreleptin and 351 received placebo.

One patient died after a diagnosis of lymphocytic leukemia approximately one month after initiating metreleptin 20 mg.

- Lymphocytic leukemia (LEPT-980236 Trial): Patient 1203 was a 67-year-old female with a medical history of obesity, on the following concomitant medications: ethinylestradiol, multivitamins, calcium, and Ascripton (Maalox-buffered aspirin). On study day 29, she was hospitalized with pneumonia and study drug was discontinued. Her WBC was 104,160 cmm, neutrophils 2%, and lymphocytes 95%. A diagnosis of lymphocytic leukemia was made. She was treated with antibiotics and chemotherapy and was discharged from the hospital to hospice care. She died 30 days later.

Reviewer comment: Of note, the patient's screening (day -5) and baseline (day 1) WBC was approximately 5 x10^9/L. Her baseline lymphocytes were 80% and baseline neutrophils were 17% (absolute neutrophil count approximately 850). No further information about this patient's medical history was provided. The confounding factor of baseline neutropenia as well as the fact that the patient was only exposed to metreleptin for one month makes it difficult to attribute the event to metreleptin.

No deaths were reported in Amgen studies LEPT-960176, LEPT-960240, LEPT-970161 (congenital leptin deficiency), LEPT-970211, LEPT-980145, LEPT-980219, and LEPT-980225; as well as Amylin studies DFA101, DFA102, and DFA102E. No deaths were reported during DFA104; however, one death in a patient randomized to placebo occurred after the completion of the trial, as described here:

- Lymphangitic adenocarcinoma of the lung (DFA104 Trial, post-completion): Patient 109001 was a 60-year-old white female with a medical history of obesity (BMI 43.4 kg/m^2), hyperthyroidism, overactive bladder, bilateral varicose veins, hypertension, sinus infection, and persistent cough, who was diagnosed with lymphangitic adenocarcinoma of the lung 36 days after the first dose of randomized study medication and 23 days after the last dose of study medication. The patient's symptoms progressed at an "alarming" rate with increased cough, dyspnea, and hypoxia. The patient received morphine for cough and dyspnea and was treated with paclitaxel and carboplatin. The patient continued to deteriorate with obvious respiratory failure and died approximately 40 days after the last study dose.

Reviewer comment: Both cancer deaths in the obesity trials occurred in patients with abnormal baseline findings that were likely evidence of pre-existing disease.

7.3.2 Nonfatal Serious Adverse Events

Patients Treated for Lipodystrophy

As of the 11 Jul 2011 data cutoff, 17 (24%) of 72 ITT patients in the NIH trials experienced a total of 40 serious adverse events, including three fatal events. The System Organ Classes with the most frequently reported serious adverse events were *Gastrointestinal Disorders* (five [6.9%] patients, including four patients with pancreatitis, one of whom also had colitis, and one patient with abdominal pain) and *Infections and Infestations* (six [8.3%] patients, including two patients with appendicitis, one patient with cellulitis, pharyngitis, and streptococcal infection, one patient with pneumonia parainfluenza viral, one patient with pneumonia, and one patient with septic shock in the setting of acute pancreatitis, described in Section 7.3.1, Deaths, above). In the four-month safety update (data cutoff 11 Jan 2013), 25 of 90 patients (27.8%) experienced a total of 58 serious adverse events, including the events from the previous data cutoff.

In the FHA101 trial, as of 07 Mar 2012, 9 (32.1%) of 28 patients experienced a total of 18 serious adverse events, including two fatal events. In the four-month safety update (data cutoff 09 Jan 2013), 10 (28.6%) of 35 patients experienced a total of 27 serious adverse events, including the events from the previous data cutoff.

The table below lists all serious adverse events in the lipodystrophy trials, up until the final data cutoffs in the four-month safety update.

Table 46. Treatment-Emergent Serious Adverse Events [NIH trials 991265 / 20010769, data cutoff 11 Jan 2013, and FHA101, data cutoff 09 Jan 2013]

Trial	Patient ID Age / Sex / Lipodystrophy Type	Relevant Medical History	Preferred Term [1]	Time to Onset (Days)	Outcome
NIH	90101 17 / F / AGL	Pancreatitis, hypertriglyceridemia (TG 7420 mg/dL), xanthoma	Pancreatitis	4084	Recovered/Resolved
			Superior mesenteric artery syndrome	4084	Recovered/Resolved
NIH	90103 27 / F / AGL	Autoimmune hepatitis, liver fibrosis, depression	Hepatic enzyme increased	481	Recovered/Resolved
			Paranoia	655	Recovered/Resolved
NIH	90105 14 / F / CGL	Hypertension (baseline BP 149/85), tachycardia (baseline HR 105), nonalcoholic steatohepatitis, proteinuria	Hypertension	0 [2]	Recovered/Resolved
NIH	90106 35 / F / CGL	Peripheral vascular disease, amputated left great toe, diabetes mellitus, deep vein	Muscular weakness	1	Recovered/Resolved
			Myoclonus	1	Recovered/Resolved
			Pain in extremity	1	Recovered/Resolved
			Respiratory distress	12	Recovered/Resolved

		thrombosis, lower extremity weakness, avascular necrosis, left shoulder pain, smoking, proteinuria (2.6 g/24 h)	Renal failure	3464	Fatal
NIH	90107 42 / F / FPL	Focal glomerulonephritis, stage IV kidney failure, proteinuria (1.9 g/24 h), coronary artery disease, multiple stent placements, stable angina, hypertension, hypertriglyceridemia, diabetes mellitus, recurrent pancreatitis	Right renal transplant	2748	Recovered/Resolved
			Cellulitits	106	Recovered/Resolved
			Pharyngitis	106	Recovered/Resolved
			Streptococcal infection	106	Recovered/Resolved
			Catheterization cardiac	2657	Recovered/Resolved
NIH	90109 13 / F / AGL	Diabetes, nonalcoholic steatohepatitis, bridging fibrosis, multiple episodes of pancreatitis, proteinuria (2.7 g/24 h), hypertriglyceridemia, xanthoma	Hypoa buminaemia	422	Not reported
			Liver disorder	422	Not reported
			Proteinuria	422	Ongoing [3]
			Pancreatitis	168	Recovered/Resolved
NIH	90110 8 / F / AGL	Asthma, frequent upper respiratory infections, IgA deficiency, Kawasaki's disease, allergic rhinitis, autoimmune hepatitis, mild portal f brosis, fatty liver, diabetes mellitus, mild proteinuria	Alanine aminotransferase increased	34	Recovered/Resolved
			Chest discomfort	194	Recovered/Resolved
			Dyspnea	194	Recovered/Resolved
			Flushing	194	Recovered/Resolved
			Panic reaction	194	Recovered/Resolved
			Pneumonia parainfluenzae viral	1021	Recovered/Resolved
NIH	90116 47 / F / CGL	Diabetes mellitus, hyperlipidemia, chronic kidney disease, renal transplant, pancreatitis, hepatic steatosis, hepatitis, cirrhosis, celiac disease	Lower gastrointestinal hemorrhage	3566	Recovered/Resolved
NIH	90121 32 / F / FPL	Pancreatitis, hypertriglyceridemia, diabetes mellitus, xanthoma, chronic abdominal pain	Pancreatitis	43	Recovered/Resolved
NIH	90125 15 / F / CGL	Pancreatitis, hypertension, baseline TG 1669 mg/dL, focal segmental glomerulosclerosis	Cardiac arrest	106	Fatal
			Pancreatitis	104	Fatal
			Septic shock	104	Fatal
NIH	90128 15 / M / AGL	Diabetes mellitus, hypertriglyceridemia, severe depression, chronic abdominal pain, nausea, vomiting, dehydration, autoimmune hepatitis, chronic transaminasemia	Abdominal pain	2032	Ongoing [4]
			Dehydration	2032	Ongoing [4]
NIH	90135 35 / F / FPL	Diabetes mellitus, benign ovarian masses, pancreatitis (recurrent severe)	Appendicitis	39	Recovered/Resolved
			Ovarian cysts	90	Recovered/Resolved
NIH	90136 23 / F / FPL	Depression (severe), attempted suicide (past suicide attempts as teenager; mother committed suicide at age 31), history of abuse and neglect as a child, adjustment disorder	Suicide attempt	~1431	Recovered/Resolved

NIH	90137 13 / F / CGL	Diabetes mellitus, pancreatitis, hypertriglyceridemia, depression, hypertension, left ventricular hypertrophy	Appendicitis	~925	Recovered/Resolved
NIH	90138 34 / F / FPL	Lipoatrophic diabetes, pancreatitis, nonalcoholic steatohepatitis, hypertriglyceridemia (TG 359 mg/dL)	Colitis	874	Recovered/Resolved
			Pancreatitis	876	Recovered/Resolved
NIH	90143 13 / F / CGL	Insulin resistance (2005), diabetes mellitus, non-alcoholic steatohepatitis, cirrhosis, hepatopulmonary syndrome	Sepsis [5]	~1497	Recovered/Resolved
NIH	90147 59 / F / AGL	Intermittent neutropenia, hepatosplenomegaly, multinodular goiter, thyroidectomy	T-cell lymphoma	233	Withdrawn from study
NIH	90151 27 / F / FPL	Diabetes, severe hypertriglyceridemia, xanthomas, hepatosteatosis, acute renal failure, pancreatitis, intermittent diarrhea, gastroparesis, chronic cholecystitis	Abdominal pain	947	Recovered/Resolved
			Ovarian germ cell teratoma	1064	Recovered/Resolved
			Lower gastrointestinal hemorrhage with anaemia	1030	Recovered/Resolved
			Anoxic encephalopathy (fatal)	1232	Fatal
NIH	90156 22 / F / CGL	Hashimoto's thyroiditis, acromegaly of the hands, severe insulin resistance, hypertriglyceridemia, vitamin D deficiency, pancreatitis, papillary thyroid cancer	Thyroid cancer	705	Recovered/Resolved
			Premature baby Maternal exposure during pregnancy	1274	Recovered/Resolved
NIH	90158 18 / F / AGL	Severe liver disease with cirrhosis, diabetes mellitus, hypercholesterolemia, mild renal insufficiency, proteinuria	Hepatic encephalopathy	344	Recovered/Resolved
			Chronic hepatic failure	523	Fatal
NIH	90164 16 / F / CGL	Cirrhosis, chronic gastritis, grade III esophageal varices, hepatic encephalopathy, diabetes with extreme insulin resistance, hypertriglyceridemia, IgA nephropathy, proteinuria, hypertension	Liver disorder (Hepatic encephalopathy)	807	Recovered/Resolved
			Liver disorder	874	Recovered/Resolved
			Abdominal pain	858	Recovered/Resolved
NIH	90168 1 / M / CGL	Viral syndrome, hypertension, hypertriglyceridemia, fatty liver, hepatomegaly	Pneumonia	98	Recovered/Resolved
NIH	90170 11 / F / AGL	Non-alcoholic steatohepatitis, hyperlipidemia, hypertriglyceridemia, severe insulin resistance	T-cell lymphoma	659	Ongoing
NIH	90180 28 / F / FPL	Chronic pancreatitis (usually in conjunction with hypertriglyceridemia of 500-14,000), extreme insulin resistance with type 2 diabetes, diabetic ketoacidosis, chronic pain disorder with opioid use	Abdominal pain (Pancreatitis chronic?)	20	Recovered/Resolved
			Abdominal pain (Pancreatitis chronic?)	108	Recovered/Resolved
			Abdominal pain	197	Recovered/Resolved

FHA101	648001 9 / F / AGL	History of acute pancreatitis, high triglycerides (10,623 mg/dL), diabetes mellitus	Pancreatitis acute	191	Recovered/Resolved
			Constipation	942	Recovered/Resolved
			Pancreatitis (with ileus)	1205	Recovering
			Diabetic ketoacidosis	1205	Recovered/Resolved
			Hypertriglyceridemia	1311	Recovering
			Hyperglycemia	1305	Recovering
FHA101	648003 58 / F / FPL	Coronary artery disease, hypertension, CABG, GERD, fatty liver, back and neck pain, lipid abnormalities, diabetes, hyperthyroidism	Chest pain	500	Recovered/Resolved
FHA101	648004 30 / F / FPL	Diabetes mellitus, hypertension, high triglycerides, fatty liver	Cellulitis	316	Recovered/Resolved
FHA101	648005 50 / F / FPL	Urinary tract infections, diabetes mellitus, hypertriglyceridemia, hypertension	Escherichia urinary tract infection	79	Recovered/Resolved
			Urinary tract infection	446	Recovered/Resolved
			Gastroenteritis	665	Recovered/Resolved
			Hypoglycemia	1157	Recovered/Resolved
			Hypotension	1156	Recovered/Resolved
			Migraine	1151	Recovered/Resolved
			Gastroenteritis	1032	Recovered/Resolved
FHA101	648008 67 / F / APL	Seizures, hypertension, coronary artery disease, two stents, peripheral vascular disease, axillofemoral bypass	Loss of consciousness	56	Fatal
FHA101	648015 62 / F / FPL	Still's disease, type 2 diabetes mellitus, atrial fibrillation, aortic atherosclerosis, CVA, acute renal failure, hypertension, lung cancer	Still's disease exacerbation	660	Recovered/Resolved
FHA101	648021 43 / F / FPL	Vertigo intermittent, myopathy, f bromyalgia, hypertension, muscle spasms, Tarui disorder (phosphofructokinase deficiency)	Vertigo positional	80	Recovered/Resolved
FHA101	649001 67 / F / AGL	Ascites, esophageal reflux, adenocarcinoma of undetermined origin	Erosive esophagitis	79	Recovered/Resolved
			Adenocarcinoma	79	Fatal
FHA101	677001 47 / F / FPL	Hyperlipidemia, hypertension, coronary artery disease, peripheral arterial disease, osteomyelitis, iron deficiency anemia	Hypoglycemia	23	Recovered/Resolved
FHA101	677002 25 / F / CGL	Diabetes mellitus, gastroparesis, cirrhosis of liver, recurrent nausea and vomiting, insulin resistance, hypertriglyceridemia, polycystic ovary, retinopathy, microalbuminuria, hypertension, diabetic neuropathy, depression	Abdominal pain	1	Recovered/Resolved
			Nausea	1	Recovered/Resolved
			Vomiting	1	Recovered/Resolved
			Diabetic gastroparesis	210	Recovered/Resolved
			Ileus	209	Recovered/Resolved
			Suicidal ideation	192	Recovered/Resolved

[1] coded using MedDRA v 13.0
[2] Event occurred after first injection of metreleptin treatment.
[3] This SAE was ongoing as of the cutoff date (31 July 2009) for the original BLA submission. Patient 90109 subsequently died of hepatorenal failure about 9 months after cessation of metreleptin treatment.

[4] The patient was hospitalized for the concurrent events, but hospital records were not available and thus, further details, including outcome, are not available. The patient was discharged from the hospital and continued participation in the study as of 11 July 2011.
[5] Reportedly no source of infection was found. Limited information was available from this hospitalization (occurred in home country of Peru).

Source: BLA 125390; Clinical Safety Update submission 27 Mar 2013, Tables 19, 20, 35, and 36

Serious Adverse Events Assessed as Related by the Investigator to Metreleptin

Two serious adverse events in the NIH trials were assessed by the investigator as related to metreleptin treatment: hypertension in Patient 90105, and respiratory distress in Patient 90106.

- The serious adverse event of hypertension and related adverse event (non-serious) of tachycardia occurred in Patient 90105, a 14-year-old patient with CGL and a history of hypertension and tachycardia at baseline. The elevation in blood pressure (195/110 mmHg) occurred after the second dose of metreleptin and was transient, with blood pressure improving to close to baseline levels (170/80 to 90 mmHg) within 15 to 20 minutes; nevertheless, the patient was hospitalized for further monitoring and evaluation. The event was assessed by the investigator as related to metreleptin, likely because of the temporal relationship to the drug administration. The event of hypertension resolved within a few days, and the patient's blood pressure improved (121/69 mmHg) over the next several months after resuming metreleptin treatment and with adjustment of blood pressure medications.

Reviewer comment: The need for adjustment in blood pressure medications is noted. The relationship to metreleptin is unclear.

- The serious adverse event of respiratory distress occurred in Patient 90106, a 35-year-old patient with CGL who had a complicated on and off therapy course due to adverse events at the beginning of metreleptin treatment and experienced an episode of respiratory distress that required hospitalization one day after restarting metreleptin for the third time. The event resolved within one day and the patient continued on therapy for another 14 months.

Two serious adverse events in FHA101 were assessed as related to treatment; both hypoglycemia events.‡‡‡‡‡‡

- At study entry, Patient 677001 was a 47-year-old white female with FPL. Relevant medical history included diabetes mellitus for 25 years (treated with U-500 insulin without prior history of problems with hypoglycemia; blood glucose values prior to starting metreleptin were in the 200-300's), hyperlipidemia, hypertension, coronary artery disease, peripheral arterial disease, osteomyelitis, and iron deficiency anemia. On 31 Mar 2011, three weeks after starting metreleptin, the patient experienced low

‡‡‡‡‡‡ The event in Patient 648005 was reclassified as "unrelated" by the investigator; however, the event is captured here for completeness.

blood glucose levels with some values being below 60 mg/dL. The patient was taking 75 units of insulin twice daily. On 01 Apr 2011, approximately 23 days after initiating metreleptin treatment, the patient experienced an event of assisted hypoglycemia. The patient was feeling hot and sweaty prior to the event. She was talking on the telephone with her brother when her speech was noted to be slurred and her brother could not understand her. The patient's neighbor, a physician's assistant, was called and found the patient in bed. The neighbor was able to arouse her, but the patient was clammy, diaphoretic and appeared tired. The neighbor reported that the patient was able to answer questions and did not appear to be postictal or have lost bowel or bladder function. No head or body contusions were noted, and it did not appear that the patient had fallen. The patient was given sips of oral carbohydrate (Pepsi); blood glucose level by finger stick 5 to 6 minutes afterwards was apparently 137 mg/dL. The patient's mental status and level of alertness appeared to improve significantly after ingestion of oral carbohydrate. The patient stabilized and did not go to the emergency room or hospital. The outcome of assisted hypoglycemia resolved on the same day. The investigator confirmed that the patient took metreleptin on the date she experienced the event. The patient continued in the trial.

- At study entry, Patient 648005 was a 50-year-old white female with FPL. Relevant medical history included hypertension, type 2 diabetes, hypothyroidism, hypercholesterolemia, hypertriglyceridemia, fatty liver, recurrent urinary tract infections, proteinuria, weakness, neuropathy, acanthosis nigricans, recurrent folliculitis, nocturia, and chronic leukocytosis. Relevant recent medical history included a hospitalization on (b) (6) for headache (migraine) and hypertensive urgency. The patient received intravenous labetalol, analgesics and compazine with improvement, and was discharged on (b) (6) with a blood pressure of 103/64 mmHg, and prescriptions for topiramate and prochlorperazine. On (b) (6), approximately 1155 days after initiating metreleptin therapy, the patient began to feel dizzy and “not with it”. Her blood pressure was 82/60 mmHg. She received intravenous fluids in the emergency room and was admitted to the hospital for observation due to refractory hypotension. The provisional diagnosis was hypotension, potentially due to a drug interaction, topiramate causing hypotension, dehydration, or medication as etiology with a thiazide diuretic. The patient’s topiramate was discontinued, and blood pressure medications were adjusted. The patient’s blood pressure improved. On (b) (6), while still hospitalized, the patient experienced a low blood sugar of 36 mg/dL at 11 pm, feeling very foggy and very unstable. She received oral carbohydrates and the hypoglycemia was reported resolved that same day. This event occurred after topiramate was discontinued, and was felt to have possibly been precipitated by the patient’s nausea or her diabetes medications, including insulin, metreleptin and metformin. The patient was discharged on (b) (6). She remained in the trial as of 09 Jan 2013.

Other Serious Adverse Events of Interest

Other serious adverse events of interest include the following (with the exception of serious adverse events of pancreatitis, which are presented separately in Section 7.3.5, Submission Specific Primary Safety Concerns, and serious adverse events of cancer, which are presented separately in Section 7.6.1, Human Carcinogenicity):

- Increased liver enzyme: At study entry, Patient 90103 (NIH Trial) was a 28-year-old white female with a 23-year history of AGL. Other relevant past medical history at study entry included diabetes, autoimmune hepatitis, liver fibrosis, and hepatosplenomegaly. At the baseline visit on 21 Aug 2000, ALT and AST were 128 and 57 U/L, respectively. Subsequent LFTs during treatment were: 84 and 40 U/L, respectively on 02 Oct 2000, 54 and 34 U/L, respectively on 14 Nov 2000, 44 and 29 U/L, respectively on 16 Jan 2001, 51 and 30 U/L, respectively on 26 Mar 2001, 124 and 75 U/L, respectively on 08 Jun 2001, 51 and 41 U/L, respectively on 29 Aug 2001, 44 and 32 U/L, respectively on 11 Oct 2001. On 28 Dec 2001, day 482 of treatment with metreleptin, the patient experienced an adverse event of increased hepatic enzymes (428 U/L). Details as to whether the elevation of 428 U/L occurred in AST or ALT are not available. The patient was not hospitalized and the adverse event was not considered life threatening but was classified as a serious adverse event due to it being an "important medical event". Metreleptin treatment was stopped on 04 Jan 2002 due to this event. The event of increased hepatic enzymes was assessed as resolved after 12 days on 09 Jan 2002. On the patient's last follow-up visit on 15 Jan 2002, ALT was 272 U/L and AST was 155 U/L. The patient resumed study medication on 14 Mar 2002 and continued treatment until 21 Jun 2002 when she was withdrawn from the study after she experienced an event of paranoia (admitted to a psychiatric hospital for "strange behavior" and "listening to voices"; diagnosed with paranoid delusions and bipolar disorder).

Reviewer comment: This is considered an event of interest because there seems to be a number of patients with AGL and baseline liver disease / autoimmune hepatitis who have liver events. The psychiatric adverse events are noted as well; see further discussion of psychiatric events in Section 7.3.5, Submission Specific Primary Safety Concerns.

- Pregnancy: At study entry, Patient 90105 (NIH Trial) was a 14-year-old white female with CGL and relevant medical history of tachycardia, non-alcoholic steatohepatitis, diabetes, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, proteinuria, and hypertension. The patient experienced a serious adverse event of worsening hypertension in Sep 2000, as described previously. On 13 Apr 2009, after approximately 7.5 years of metreleptin treatment, the patient received confirmation of pregnancy (date of last menstrual period was unknown). At that time, the gestational age was eight weeks with an estimated date of delivery of 25 Nov 2009. The method of contraception at the time of conception was condoms. No adverse

events had been reported. After thorough consideration of the benefits versus risks to both the mother and fetus, the investigator consulted with the patient and her mother and the decision was made to continue metreleptin therapy and study participation. Additional information received from the investigator on 15 Jul 2009 indicated that the patient remained metabolically stable and the pregnancy was uneventful to that point. The patient initiated Novorapid insulin 75 units daily on 06 Aug 2009 and had titrated to 180 units of insulin daily by 10 Oct 2009. On 30 Oct 2009 (37 weeks of gestation), the patient was gaining the appropriate amount of weight and required 180 units of insulin a day to maintain her target blood glucose. On (b) (6), the patient delivered a 9.5 pound, 22 inch male infant via vaginal delivery. Novorapid was discontinued upon delivery. An episiotomy was performed, which was not considered by the investigator to be an adverse event. The baby was born as a stillbirth with Apgars of 0 and 0, but was successfully resuscitated after full code efforts. After delivery, it was noted that the infant had weakness and limitation of movement of his left arm. The infant was transferred to the NICU and later diagnosed with shoulder dystocia and Erb's palsy. The patient continued metreleptin therapy, began breastfeeding the infant, and continued to breastfeed until 01 Apr 2010. The infant underwent physical therapy with improvement and increased strength of the left arm. At the time of the last follow-up information from the investigator, the infant was a healthy and well-developing 5-month-old with improving Erb's palsy. The stillbirth and shoulder dystocia were assessed as secondary to the vaginal delivery, large for gestational age (from maternal gestational diabetes), and had become caught in the birth canal with resultant traumatic birth injury. Of note, the infant had drug exposure during pregnancy as well as via breast milk.

- Chronic renal failure: At study entry, Patient 90107 (NIH Trial) was a 42-year-old white female with FPL. Other relevant past medical history at study entry included focal glomerulonephritis, proteinuria, stage 4 kidney failure since 1999, hypertension, hypertriglyceridemia, hepatomegaly, and diabetes mellitus. At baseline, the patient's serum creatinine was 1.6 mg/dL (27 Nov 2000). On 03 Dec 2000, 24-hr urine protein was 1891.7 mg. The patient's serum creatinine ranged from 1.3 to 2.1 mg/dL through year 3 of treatment. Between three to five years of treatment, serum creatinine ranged from 2.3 to 2.7 mg/dL. On 13 Nov 2006 (month 68 of metreleptin treatment), serum creatinine was 4.7 mg/dL. Twenty-four hour urine protein results were 2208 mg, 1840 mg, 2252 mg, 739 mg, 473 mg, at years 1, 2, 3, 4, and 5, respectively and 819 mg on 14 Nov 2006. In Nov 2007, the patient developed end-stage renal disease requiring peritoneal dialysis. On (b) (6), after approximately 7.5 years of metreleptin treatment, the patient underwent a right renal transplant. The patient continued taking metreleptin and participating in the study following the renal transplant.

- Hypoalbuminemia, worsening of proteinuria, and worsening of liver disease: At study entry, Patient 90109 (NIH Trial) was a 13-year-old white female with a seven-

year history of AGL. Relevant past medical history at study entry included type 1 diabetes, polyuria, hypertriglyceridemia, hepatomegaly, bridging fibrosis, non-alcoholic steatohepatitis, pancreatitis, proteinuria, and albuminuria. The patient initiated treatment with metreleptin on (b) (6). This patient also experienced a serious adverse event of pancreatitis on 25 Feb 2002 (see the description of the event in Section 7.3.5, Submission Specific Primary Safety Concerns). At baseline on 04 Sep 2001, the patient's ALT and AST were 79 U/L and 85 U/L, respectively, with an albumin of 3.8 g/dL and total bilirubin of 0.2 mg/dL. During the first year of metreleptin treatment, ALT ranged from 75 to 185 U/L, AST ranged from 110 to 190 U/L, albumin ranged from 3.4 to 4.4 g/dL, and total bilirubin ranged from 0.3 to 1.2 mg/dL. On 26 Sep 2002, ALT rose to 445 U/L and AST to 479 U/L while albumin decreased to 2.6 g/dL and total bilirubin remained stable at 0.7 mg/dL. On (b) (6) (b) (6), after 424 days of treatment with metreleptin, the patient had a marked elevation in liver enzymes (AST 1159 U/L and ALT 300 U/L) with low serum albumin (1 g/dL) and rising total bilirubin (2 mg/dL). The patient was admitted to the hospital. She was noted to have massive proteinuria (24-hr protein excretion of 20 g) compared to baseline 24-hr urine protein excretion which ranged between 2-4 g per day. An adverse event of membranoproliferative glomerulonephritis (MPGN) was reported on (b) (6). The patient was treated with human albumin, furosemide, metolazone, lisinopril, spironolactone, and vitamin K. Within several days of admission, the liver abnormalities improved whereas the proteinuria continued. The patient was also diagnosed with alpha hemolytic streptococcal infection during this admission and received ceftriaxone treatment. The events of hypoalbuminemia and worsening proteinuria and liver disease were attributed to the patient's underlying kidney and liver disease. Pioglitazone therapy had been discontinued 30 Oct 2002 and was not restarted. Metreleptin was discontinued on 27 Nov 2002, and the patient was withdrawn from the study on 02 Dec 2002. The event of proteinuria had not resolved by 02 Dec 2002. Per follow up information received from the investigator on 15 May 2007, the patient died due to hepatorenal failure nine months after stopping metreleptin therapy (exact date not provided). The patient apparently needed both a kidney and a liver transplant, but was never officially placed on a transplant list.

Reviewer comment: As described in Section 7.3.3, Dropouts and/or Discontinuations, this patient was discontinued from the trial due to "health issues" (not considered an adverse event). No details were provided regarding the diagnosis of MPGN (i.e., renal biopsy). As noted in a 2004 NIH publication that described this patient's case, it is possible that metreleptin could have exacerbated MPGN this patient.[30] Notably, she had AGL, an autoimmune condition. The cause for the acute rise in transaminases in this patient is unknown.

- Alanine aminotransferase increased: At study entry, Patient 90110 (NIH Trial) was an 8-year-old white female with a two year history of AGL. Other relevant past

medical history at study entry included hepatosplenomegaly, mild portal fibrosis and regenerative hyperplasia in liver, fatty liver, autoimmune hepatitis, hypertriglyceridemia, Hashimoto thyroiditis, Kawaski's disease, and type 2 diabetes.[§§§§§§§] At Visit 1 on 27 Nov 2001, the patient's ALT was 53 U/L and AST was 39 U/L. On 02 Jan 2002, day 35 of treatment with metreleptin, the patient experienced an increased ALT of 230 U/L. Two days later, the ALT level was 317 U/L. The event of increased ALT resolved on 10 Jan 2002. Laboratory tests on 05 Feb 2002 revealed that the ALT had decreased to 48 U/L. Study medication was discontinued five days after the event occurred on 07 Jan 2002. The patient restarted metreleptin treatment on 09 Feb 2002 at the same starting dose of 0.3 mg BID, which was subsequently titrated to 0.55 mg BID on 02 Apr 2002. Liver enzymes remained stable upon reinitiation of metreleptin with ALT of 48 U/L and AST of 30 U/L on 08 Apr 2002. Of note, the patient also experienced adverse events of influenza and upper respiratory tract infection on 02 Jan and 04 Jan 2000, respectively. The investigator's opinion was that the event of elevated ALT was likely related to the patient's underlying illness of autoimmune hepatitis.

Reviewer comment: This serious adverse event is included as an event of interest, due to the possibility of an exacerbation of the patient's autoimmune disease (autoimmune hepatitis). It is noted that the patient was able to restart metreleptin therapy and transaminases remained stable.

- Hepatic encephalopathy (Patient 90158, NIH Trial); see the description of this serious adverse event in Section 7.3.1, Deaths.

- Still's disease exacerbation: At study entry Patient 648015 (FHA101 Trial) was a 62-year-old white female with an approximate two year history of lipodystrophy (FPL). Relevant medical history included Still's disease, type 2 diabetes, atrial fibrillation, cerebrovascular accident, acute renal failure, hypertension, cholecystectomy, and lung cancer with removal of the center right lobe. Approximately 660 days after initiating metreleptin treatment, the patient presented with pleuritic chest pain. Chest x-ray and CT of the chest were negative for dissection and pulmonary arterial thromboembolism. An echocardiogram showed a small pericardial effusion and normal left ventricular function. Cardiac enzymes were negative. ESR was 34 and C-reactive protein was 4.0 (units not provided). Rhematology was consulted and diagnosed the patient's pain as related to her Still's disease. She was discharged on anakinra and celecoxib. Metreleptin was stopped for three days during the hospitalization. The event did not reappear after reintroduction of metreleptin. The patent continued participation in the trial.

[§§§§§§§] A subsequent serious adverse event also noted that she had a medical history of immunoglobulin A deficiency causing frequent upper respiratory infections, and asthma.

Reviewer comment: This is an event of interest because leptin might exacerbate autoimmune diseases. It is noted that the event did not reappear after metreleptin was restarted.

- Suicide attempt: At study entry, Patient 90136 (NIH Trial) was a 23-year-old Asian female patient with FPL. Relevant past medical history at study entry included past suicide attempts as a teenager, depression, diabetes, and hypertriglyceridemia. At the patient's annual visit to the NIH clinical study site in July 2011 (approximately year 5), the patient told the NIH physician that she was admitted to a psychiatric hospital in (b) (6) (approximately year 4) for an attempted suicide by drug overdose. The patient was hospitalized for six weeks. During the hospitalization, her citalopram was increased to 80 mg, and her anxiety was greatly decreased with the increased citalopram dose. Remeron was administered during the hospitalization and she was discharged on Seroquel 50 mg PRN for panic attacks. The patient stated the reason for attempted suicide was because she 'struggled with what her illness allows her to do in life and struggles with depression and low self-esteem'. The patient was discharged from the hospital on an unspecified date in (b) (6) (b) (6) and the event of attempted suicide was considered resolved in September 2010. It is unknown if the patient missed metreleptin study medication during the hospitalization. Since being discharged from the psychiatric hospital, the patient denied feeling suicidal and her depressive symptoms as well as anxiety and panic symptoms were well-controlled with medication. The patient reported meeting with a psychiatrist for talk therapy and medication adjustment every two weeks. The investigator stated that during a Jul 2011 NIH clinical study site visit with a social worker, the patient was noted to be psychiatrically stable. Study medication was ongoing and the patient continued participation in the study as of the data collection cutoff date of 11 Jul 2011.

- Suicidal ideation: At study entry, Patient 677002 (FHA101 Trial) was a 25-year-old white female with CGL. Relevant medical history included a prior suicide attempt (unknown date) with no regular psychiatric follow-up in years, diabetes mellitus, gastroparesis, diabetic neuropathy, recurrent nausea and vomiting, and history of food bezoar on endoscopy (Apr 2010). Other medical history included compensated cirrhosis (since 14 years of age; on transplant list since 2001), hypertriglyceridemia, polycystic ovary, retinopathy, microalbuminuria, hypertension, insulin resistance, cholecystectomy, tobacco user (less than one pack per day), and depression. On (b) (6), approximately 195 days after starting metreleptin treatment, the patient experienced suicidal ideation. The patient's mother reported the patient had had suicidal ideation for the past two weeks and had been taken to the emergency room (b) (6) and was given Xanax and discharged without being admitted. The event was considered resolved on 07 Dec 2011. It is unknown if any doses of study medication were missed due to this event. The patient was withdrawn from the study on 07 Dec 2011 by investigator decision (due to family conflict, personal issues, missed appointments, and non-compliance at times).

- Pre-term delivery of non-viable fetus: At study entry, Patient 90156 (NIH Trial) was a 22-year-old Hispanic female with CGL. Relevant medical history included type 2 diabetes, insulin resistance, hypertriglyceridemia, pancreatitis, Hashimoto's thyroiditis, and vitamin D deficiency. The patient experienced a serious adverse event of papillary thyroid cancer in April 2011 for which she underwent thyroidectomy, followed by radioiodine treatment in January 2012 (see narrative in Section 7.6.1, Human Carcinogenicity). This was a retrospectively reported pregnancy case. Information regarding the date of the last menstrual period was not provided. The patient received study drug from conception (approximately (b) (6) (b) (6) based on gestational age) until week 20 of gestation. On (b) (6), after 3.5 years of treatment with metreleptin, the patient was hospitalized due to several days of abdominal pressure during pregnancy. On examination, she had bulging membranes, cervical effacement, and was 1.5 cm dilated. Ultrasound showed approximately 2 cm cervical dilation. The patient was kept on bed rest but continued to dilate. She was given a choice of rescue cerclage, expectant management, or induction termination. She chose cerclage, however, on (b) (6), prior to the procedure, she had membrane rupture. On ultrasound, the fetal legs and part of the abdomen were found to be prolapsing through the cervix. The patient was transferred to labor and delivery, given misoprostol, and delivered the infant via spontaneous vaginal delivery. The infant (female) was born alive and apparently normal for a gestational age of 20 weeks and four days. Birth weight and length were not provided. No resuscitation was attempted, and the expected neonatal demise ensued. The patient's post-delivery course was uncomplicated. She remained afebrile, with no lymphocytosis, and her urinalysis, tests for gonorrhea and Chlamydia, and wet mount were negative throughout hospitalization. Based on clinical examination, she was treated for bacterial vaginosis with metronidazole. She was discharged on (b) (6) and the event of premature delivery was reported resolved. Metreleptin treatment was ongoing and the patient continued participation in the study as of the data cutoff date of 11 Jan 2013.

- Worsening of advanced liver disease (two events): At study entry, Patient 90164 (NIH Trial) was a 16-year-old female of unspecified race with a history of CGL. Relevant medical history included hypertension, cardiomyopathy with pulmonary stenosis, moderate concentric left ventricular hypertrophy with diastolic dysfunction, gastritis, grade III esophageal varices, diabetes with extreme insulin resistance, hyperlipidemia, hypertriglyceridemia, hepatic steatosis with cirrhosis, portal hypertension, hepatic encephalopathy, proteinuria, IgA nephropathy, iron deficiency anemia, and developmental delay. On (b) (6), after approximately 2.2 years of treatment with metreleptin, the patient presented to the emergency room with slightly altered mental status, mild diffuse pruritic rash, and a three month history of increasing abdominal pain and distension. She was hospitalized and reported to have hepatic encephalopathy with an elevated ammonia of 146, lipase 38, lactate 1.6, AST 71, and ALT 63 (units, reference ranges and date obtained not provided).

This was felt by her local physicians to be temporally related to the patient's metformin therapy. Metformin was discontinued and the patient's condition improved. Metreleptin was not interrupted. A CT scan of the abdomen and pelvis on an unspecified date was compared to a prior CT of December 2009 and showed persistent and slightly progressive hepatosplenomegaly (consistent with cirrhosis and portal hypertension); unchanged kidney enlargement; gallbladder swelling without gallstones; and prominent bladder distention. The patient's pain improved after placement of a Foley catheter and administration of lactulose. She was discharged on (b) (6) and the event, reported as worsening of advanced liver disease, was considered resolved. The patient continued trial participation. On (b) (6) (b) (6), the patient again was admitted to the hospital with decreased responsiveness, abdominal pain, and fever. A chest x-ray obtained on admission revealed possible pneumonia. A CT scan of the abdomen (date not specified) showed little change from her previous scan. She was reported to have elevated serum ammonia levels and a negative urinalysis. She was treated with levofloxacin and her condition improved. She was discharged on (b) (6) with discharge diagnoses including hepatic encephalopathy, abdominal pain, pneumonia, and fever. The event, reported as worsening of advanced liver disease, was considered resolved on that date. Study medication was ongoing and the patient continued trial participation as of the data cutoff date of 11 Jan 2013.

Patients Treated for Obesity

The following table enumerates the serious adverse events from the five Amgen trials included in the ISS. In this table, all doses of metreleptin are merged. The ITT Population consists of all patients who received at least one dose of randomized study medication (metreleptin or placebo) during the trial. For trial LEPT-970213, in which eligible patients were randomized into a 24-week treatment period after a four-week metreleptin (10 mg twice daily) induction period, all 228 patients who received at least one dose of metreleptin during the metreleptin induction period are counted as metreleptin-treated patients in the table. Among these 228 patients, 189 patients were randomized to treatment (126:63 metreleptin:placebo) and underwent a 24-week treatment period; those 63 patients randomized to placebo are counted as both metreleptin-treated and placebo-treated, and the analysis were conducted as appropriate depending on the period when data were collected.

Table 47. Incidence of Serious Adverse Events, Population: Obesity ISS Intent-to-Treat (N = 1072)

	Placebo N=351 n (%)	Metreleptin N=784 n (%)
All Serious Adverse Events	13 (3.7)	16 (2.0)
Cardiac disorders	0	4 (0.5)
Angina pectoris	0	2 (0.3)
Atrial fibrillation	0	1 (0.1)
Ventricular arrhythmia	0	1 (0.1)
Gastrointestinal disorders	2 (0.6)	1 (0.1)
Abdominal pain upper	1 (0.3)	1 (0.1)
Pancreatitis	0	1 (0.1)
Diverticulum intestinal	1 (0.3)	0
Rectal hemorrhage	1 (0.3)	0
General disorders and administration site conditions	4 (1.1)	1 (0.1)
Injection site erythema	0	1 (0.1)
Chest pain	2 (0.6)	0
Pyrexia	1 (0.3)	0
Vessel puncture site reaction	1 (0.3)	0
Hepatobiliary disorders	1 (0.3)	0
Cholelithiasis	1 (0.3)	0
Jaundice	1 (0.3)	0
Infections and infestations	3 (0.9)	4 (0.5)
Chronic sinusitis	0	1 (0.1)
Pneumonia	1 (0.3)	1 (0.1)
Sinusitis	0	1 (0.1)
Upper respiratory tract infection	0	1 (0.1)
Injection site abscess	1 (0.3)	0
Meningitis meningococcal	1 (0.3)	0
Injury, poisoning and procedural complications	1 (0.3)	2 (0.3)
Arthropod bite	0	1 (0.1)
Tendon rupture	0	1 (0.1)
Road traffic accident	1 (0.3)	0
Investigations	2 (0.6)	1 (0.1)
Heart rate irregular	1 (0.3)	1 (0.1)
Blood pressure increased	1 (0.3)	0
Metabolism and nutrition disorders	1 (0.3)	0
Hyperglycemia	1 (0.3)	0
Musculoskeletal and connective tissue disorders	0	1 (0.1)

	Placebo N=351 n (%)	Metreleptin N=784 n (%)
Pain in extremity	0	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6)	3 (0.4)
Lymphocytic leukemia	0	1 (0.1)
Metastatic malignant melanoma	0	1 (0.1)
Uterine leiomyoma	0	1 (0.1)
Breast cancer stage III	1 (0.3)*	0
Cervix carcinoma	1 (0.3)*	0
Nervous system disorders	0	3 (0.4)
Cerebrovascular accident	0	1 (0.1)
Cubital tunnel syndrome	0	1 (0.1)
Headache	0	1 (0.1)
Renal and urinary disorders	0	1 (0.1)
Stress urinary incontinence	0	1 (0.1)
Reproductive system and breast disorders	1 (0.3)	0
Ovarian cyst	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)
Asthma	0	1 (0.1)
Surgical and medical procedures	1 (0.3)	0
Cholecystectomy	1 (0.3)	0
*Note: these events occurred in study 980236 (notably not during the randomized portion of study 970213, in which all patients received metreleptin during a run-in period; therefore, neither of these patients were exposed to metreleptin).		

Source: ISS Supporting Data Summary 5.3; version 22 Oct 2010

The narrative for the metreleptin-treated patient with the serious adverse event of pancreatitis is below:

- Patient 17022 (Amgen trial LEPT-970171) was an obese 44-year-old black female with type 2 diabetes treated with glyburide who reportedly had TG values prior to receiving randomized study medication (metreleptin 10 mg BID) ranging from 261 mg/dL to 480 mg/dL. On approximately study day 85, the patient reported stomach cramps. Ten days later, her blood glucose was 165 mg/dL and triglycerides 822 mg/dL. The stomach cramps worsened and the patient was hospitalized three days later. The patient was diagnosed with pancreatitis and treated with intravenous dextrose, sodium chloride, morphine, insulin, and metamucil. She was discharged from the hospital five days later.

The narrative for the metreleptin-treated patient with the serious adverse event of malignant melanoma is below (the other notable malignancy serious adverse event, lymphocytic leukemia, is described above in section 7.3.1, Deaths):

- Patient 15020 (Amgen trial 970171) was a 68-year-old male with type 2 diabetes and hyperlipidemia prior to receiving randomized study medication (metreleptin 10 mg BID). The patient had a history of oral carcinoma five years prior and chest melanoma one year prior, both surgically treated. On study day 101, it was noted that the patient had a firm axillary lymph node. The patient completed the study and the last dose of study drug was study day 112. A biopsy performed 34 days later revealed malignant melanoma. No further information was provided.

Reviewer comment: In addition, note that there were two cancer serious adverse events in placebo-treated patients: events of breast and cervical cancer.

The narrative for the metreleptin-treated patient with serious adverse events of cerebrovascular accident and ventricular arrhythmia is below:

- Patient 13036 (Amgen trial 970171) was a 51-year-old male with type 2 diabetes, obesity, and history of unstable blood pressure prior to receiving randomized study medication (metreleptin 20 mg). On study day 112, he complained of lightheadedness; his blood pressure was 140/98 and heart rate was 96. A mild occipital stroke was diagnosed, he was hospitalized, and study drug was discontinued. The following day, while hospitalized, he developed ventricular tachycardia, which prolonged hospitalization. The tachycardia resolved before discharge two days later.

The following table lists the serious adverse events in patients randomized in the Amgen trials not included in the ISS as well as the Amylin metreleptin + pramlintide for obesity clinical program.

Table 48. Treatment Emergent Serious Adverse Events for Patients Receiving Metreleptin from the Amgen Metreleptin Obesity Program and the Metreleptin + Pramlintide Obesity Program

Preferred Term	Metreleptin	Placebo
	n (%)	n (%)
Amgen LEPT-960176 (N=151)	**n=151**	**N/A**
Breast Neoplasm Malignant	1(0.7)	N/A
Urinary Incontinence	1 (0.7)	N/A
Amgen LEPT-960240 (N=30)	**n=23**	**n=7**
Somnolence	1 (4.3)	0
Amgen LEPT-970211 (N=6)	**n=5**	**n=1**
Asthenia	1 (20.0)	0 (0.0)
Fever	1 (20.0)	0 (0.0)
Headache	1 (20.0)	0 (0.0)
Meningitis	1 (20.0)	0 (0.0)
Vertigo	1 (20.0)	0 (0.0)
Thinking Abnormal	1 (20.0)	0 (0.0)
AMGEN LEPT-950272 (N=250)	**n=177**	**n=73**
Dyspnea	1 (0.6)	0 (0.0)
Fatigue	1 (0.6)	0 (0.0)
Nausea	1 (0.6)	0 (0.0)
Palpitation	1 (0.6)	0 (0.0)
Amgen LEPT-970161 (N=4)	**n=4**	**N/A**
Gastroenteritis Viral	1 (25.0)	N/A
DFA101 (N=83)	**n=83**	**N/A**
Myocardial Infarction	1 (1.2)	N/A
Hypersensitivity	1 (1.2)	N/A
Deep Vein Thrombosis	1 (1.2)	N/A
DFA102 (N=531)	**n=456**	**n=75**
Lymphadenopathy	1 (0.2)	0 (0.0)
Cardiac Arrest	1 (0.2)	0 (0.0)
Goitre	1 (0.2)	0 (0.0)
Non-Cardiac Chest Pain	0 (0.0)	1 (1.3)
Food Allergy	0 (0.0)	1 (1.3)
Papillary Thyroid Cancer	1 (0.2)	0 (0.0)
Parathyroid Tumor Benign	1 (0.2)	0 (0.0)
Cervicobrachial Syndrome	0 (0.0)	1 (1.3)
Convulsion	1 (0.2)	0 (0.0)
Syncope Vasovagal	1 (0.2)	0 (0.0)
Hypertension	0 (0.0)	1 (1.3)
DFA102E (N=273)	**n=242**	**n=31**
Staphylococcal Infection	1 (0.4)	0 (0.0)
Muscle Strain	1 (0.4)	0 (0.0)
Cardiac Enzymes Increased	1 (0.4)	0 (0.0)
Papillary Thyroid Cancer	1 (0.4)	0 (0.0)
DFA103 (N=78)	**n=78**	**N/A**
Breast cancer	1 (1.3)	N/A
DFA104 (N=72)	**n=36**	**n=36**
Coronary Artery Disease	1 (2.8)	0 (0.0)

Note: No serious adverse events were reported for Amgen Studies LEPT-970121, LEPT-970161, LEPT-980219, LEPT-980225, LEPT-980145, and LEPT-980298.

n = number of subjects who experienced the adverse event.

Source: 2013-05-24-bms986109-response-fda-metreleptin-clinical-q1, Attachment 1-Table 1.

Serious adverse events of cancer (breast cancer, Amgen trial LEPT-960176, Patient 01002; papillary thyroid carcinoma, Amylin trial DFA102, Patient 135036; and papillary thyroid carcinoma, Amylin trial DFA102E, Patient 137027) are described in Section 7.6.1, Human Carcinogenicity. Additional serious adverse events of interest are described briefly below:

- Cardiac Arrest and Convulsion (Amylin Trial DFA102; Patient 103011): This patient was a 47-year-old obese white female with a history of vasovagal syncope, vasovagal response secondary to stress, seizures, and blackout episodes since childhood. On Day 60 of metreleptin treatment, the patient was found seizing in her bathroom and was taken to the emergency department where the patient experienced bradycardia and a subsequent nine second episode of asystole. CPR regained a cardiac rhythm. A 10 second syncopal episode followed, resulting in a seizure. The patient was transferred to the intensive care unit for IV fluids and diagnostic testing. Computed tomography, magnetic resonance imagining, chest and spinal x-rays were normal. An electrophysiological study was performed followed by pacemaker insertion. An electroencephalogram revealed a small sharp spike in the right temporal region of questionable clinical significance, but an epliletiform process could not be ruled out.

- Allergic Reaction (Hypersensitivity) (Amylin Trial DFA101; Patient 40431): This patient was a 33-year old obese Asian female with an unremarkable medical history at study entry. On Day 29 of metreleptin therapy, the patient experienced a moderate reaction consisting of itching and hives. Diphenhydramine was administered, the event resolved and study medication was continued. On Day 56 of metreleptin therapy, the patient experienced a reaction consisting of swollen face, hives, and difficulty breathing and concentrating. The patient was seen at an emergency room and admitted overnight for observation with discharge the next day. Study medication was discontinued.

- Meningitis (Amgen Trial LEPT-970211; Patient 1107): This was a 52-year-old male who enrolled in the metreleptin intrathecal trial. A Port-A-Cath was implanted on 20 Nov 1998 and was shown to be situated in the epidural space seven days after implant. The catheter and port were replaced after 14 days and study medication began to be administered 13 days after replacement. On 29 Jan 1999, 44 days after starting study medication, the catheter was dislodged and was replaced, together with the port; study drug was administered successfully on 01 Feb 1999 and 04 Feb 1999. On 05 Feb 1999 the patient complained of "feeling moisture" on his lower back and felt that the catheter was falling out. Meningitis was confirmed with CSF culture and IV cefotaxime initiated. Three days later, the patient was still experiencing headache and fever and was withdrawn from the trial. The investigator attributed the infection to the device.

7.3.3 Dropouts and/or Discontinuations

Patients Treated for Lipodystrophy

In the NIH trials, the most common reason for withdrawal was "other" for eight (11.1%) patients: one due to "stress"[********], one due to "health issues"[††††††††], and six transferred to Named Patient Programs (compassionate use programs) in their respective countries. Four patients (5.6%) discontinued due to "noncompliance". Two patients withdrew because they were deemed ineligible to continue participation in the trial, including one patient (90115) due to a diagnosis of peripheral T-cell lymphoma and one patient (90126) due to the investigator's assessment that the patient was no longer appropriate to continue in the study due to the need to undergo other treatment for an adverse event (i.e., deep vein thrombosis). A total of five patients withdrew due to "adverse events", including deaths. Two patients (90147 and 90114) were withdrawn due to an adverse event (peripheral T-cell lymphoma and proteinuria[‡‡‡‡‡‡‡‡], respectively; the narrative for Patient 90147 is provided in Section 7.6.1, Human Carcinogenicity and the narrative for Patient 90114 is provided below). Three patients experienced serious adverse events that led to death (see Section 7.3.1, Deaths): Patient 90125, pancreatitis with a ruptured pseudocyst, leading to septic shock and subsequent cardiac arrest; Patient 90106, renal failure and subsequent cardiac arrest; and Patient 90158, chronic hepatic failure. One additional withdrawal due to death [anoxic encephalopathy, Patient 90151 (see Section 7.3.1, Deaths)] was reported in the four-month safety update.

Reviewer comment: Although only five patients were considered withdrawal due to adverse events, "stress" in Patient 90105, "health issues" in Patient 90109, peripheral T-cell lymphoma in Patient 90115 and deep vein thrombosis in Patient 90126, could be considered withdrawals due to adverse events as well.

[********] The comments available for this patient's disposition are as follows: *Pt. having psychiatric difficulties – stress at home and living situation which was affecting her ability to comply to any medical regimen or advice*

[††††††††] Patient 90109 was a 13-year old female at study entry with AGL. The patient was withdrawn from the study by the PI approximately 15 months after initiating the trial due to health issues (further details not provided, but medical history for this patient included steatohepatitis, hepatic fibrosis, pancreatitis, proteinuria, and severe hypertriglyceridemia with baseline TG 2984 mg/dL). It is noted that she had the following serious adverse events during the trial that were described in Section 7.3.2, Serious Adverse Events: pancreatitis, hypoalbuminemia, worsening of proteinuria, and worsening of liver disease.

[‡‡‡‡‡‡‡‡] Although five of 72 patients were reported to have withdrawn due to treatment-emergent adverse events in the Clinical Safety Update, during data review for the four-month safety update data cut (11 Jan 2013), it was discovered that Patient 90114 had not withdrawn from the NIH trial but had transferred to a Named Patient Program (non-US, compassionate-use) in July 2009. This patient was erroneously reported as having been withdrawn from the trial due to proteinuria. Nevertheless, the adverse event described a rapid progression of renal disease and the narrative is provided here for completeness. Follow-up on this patient in the Named Patient Program was not provided.

- Proteinuria: At trial entry, Patient 90114 was a 35-year-old male from Madagascar with a 32-year history of AGL. Other relevant past medical history at trial entry included chronic renal failure, proteinuria, hematomegaly, pancreatitis, steatohepatitis, fatigue, hypertriglyceridemia, and type 2 diabetes. At baseline (May 2002), the patient had a serum creatinine of 1.0 mg/dL, with a 24-hr urine protein excretion rate of 2450 mg per 24 hrs. Follow-up tests at the Month 4 visit (23 Sep 2002) showed a serum creatinine of 1.6 mg/dL and 24-hr urine protein excretion rate of 4100 mg per 24 hrs, and at the Month 8 visit (Feb 2003) a serum creatinine of 2.2 mg/dL and 24-hr urine protein excretion rate of 8845 mg per 24 hrs. On 07 Feb 2003, Day 271 of treatment with metreleptin, the patient was withdrawn because of the worsening proteinuria. The event was not considered a serious adverse event. The patient started dialysis nine months after he stopped metreleptin treatment.

Reviewer comment: This appears to be a very rapid progression of MPGN to end stage renal disease. This case is similar to Patient 90109, also with AGL, who developed worsening renal disease (MPGN) on metreleptin. Both cases are described in a 2004 NIH paper, which noted that the contribution of metreleptin cannot be excluded.[30]

In the FHA101 trial, as of the 07 March 2012 data cutoff, 20 of 28 patients were still actively participating. The most common reasons for withdrawal were withdrawal of consent and adverse event (three [11%] patients each). Reasons for withdrawal of consent were desire to get pregnant (Patient 648004), reason unspecified (Patient 648007), and travel burden coupled with lack of efficacy (Patient 648013). Of the three withdrawals due to adverse events, two had a fatal outcome. Patient 648008 experienced a serious adverse event, “loss of consciousness”, which had a fatal outcome (acute bilateral subdural hematomas after a fall). Patient 649001 experienced a serious adverse event of adenocarcinoma, which was a known condition prior to starting metreleptin and which had a fatal outcome. See Section 7.3.1, Deaths, for narratives of both of these events. Patient 648021 was withdrawn due to a non-serious event of muscle spasms, which was assessed by the investigator as related to treatment. In the four-month safety update, no additional patient from trial FHA101 withdrew due to an adverse event.

Patients Treated for Obesity

Withdrawals due to adverse events in the five integrated Amgen trials (ISS) occurred in 79 (10.1%) of 784 metreleptin-treated patients and 20 (5.7%) of 351 placebo-treated patients. The majority of withdrawals due to adverse events in patients treated with metreleptin were due to injection site reactions [38 (4.8%) versus one (0.3%) for placebo] and inflammatory injection-site adverse events including the preferred terms “injection site inflammation”, “injection site pruritus”, “injection site erythema”, and “injection site urticarial” [combined incidence 11 (1.4%) versus 0 (0.0%) for placebo].

Table 49. Incidence of Treatment-Emergent Adverse Events Leading to Withdrawal Summarized by System Organ Class and Preferred Term (Including Preferred Terms with Metreleptin Incidence Greater than Placebo)

System Organ Class Preferred Term	Pbo N=351	Metreleptin N=784
All AEs Leading to Withdrawal	20 (5.7)	79 (10.1)
Eye disorders	0	1 (0.1)
Eye swelling	0	1 (0.1)
Gastrointestinal disorders	2 (0.6)	4 (0.5)
Abdominal pain	0	2 (0.3)
Nausea	1 (0.3)	2 (0.3)
Abdominal distension	0	1 (0.1)
Irritable bowel syndrome	0	1 (0.1)
Pancreatitis	0	1 (0.1)
General disorders and administration site conditions	7 (2.0)	53 (6.8)
Injection site reaction	1 (0.3)	38 (4.8)
Fatigue	0	6 (0.8)
Injection site inflammation	0	4 (0.5)
Injection site pruritus	0	4 (0.5)
Injection site discoloration	0	2 (0.3)
Injection site erythema	0	2 (0.3)
Injection site urticaria	0	2 (0.3)
Chills	0	1 (0.1)
Feeling abnormal	0	1 (0.1)
Injection site vesicles	0	1 (0.1)
Malaise	0	1 (0.1)
Edema	0	1 (0.1)
Swelling	0	1 (0.1)
Infections and infestations	4 (1.1)	5 (0.6)
Hepatitis C	0	1 (0.1)
Influenza	0	1 (0.1)
Lower respiratory tract infection	0	1 (0.1)
Upper respiratory tract infection	0	1 (0.1)
Injury, poisoning and procedural complications	0	1 (0.1)
Arthropod bite	0	1 (0.1)
Metabolism and nutrition disorders	1 (0.3)	2 (0.3)
Decreased appetite	0	1 (0.1)
Musculoskeletal and connective tissue disorders	0	2 (0.3)
Osteoarthritis	0	1 (0.1)
Rotator cuff syndrome	0	1 (0.1)
Neoplasms benign, malignant and unspecified	0	1 (0.1)

Uterine leiomyoma	0	1 (0.1)
Nervous system disorders	1 (0.3)	3 (0.4)
Balance disorder	0	1 (0.1)
Dizziness	0	1 (0.1)
Dysgeusia	0	1 (0.1)
Pregnancy, puerperium and perinatal conditions	0	1 (0.1)
Pregnancy	0	1 (0.1)
Psychiatric disorders	0	2 (0.3)
Depression	0	2 (0.3)
Reproductive system and breast disorders	1 (0.3)	1 (0.1)
Menopausal symptoms	0	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.3)	12 (1.5)
Urticaria	1 (0.3)	8 (1.0)
Rash	0	2 (0.3)
Angioedema	0	1 (0.1)
Circumoral edema	0	1 (0.1)
Psoriasis	0	1 (0.1)

Source: ISS Supporting Data Summary 5.4; version 22 Oct 2010

The table below presents the number of patients with adverse events leading to withdrawal for the Amgen trials not included in the ISS and the Amylin metreleptin + pramlintide for obesity clinical program. Narratives for two events are provided above: (1) meningitis reported in Amgen trial LEPT-970211 and (2) hypersensitivity in Amylin trial DFA101, and one case of papillary thyroid cancer in DFA102 is discussed in Section 7.6.1, Human Carcinogenicity.

In addition, there were several reports related to injection site reactions in the Amgen LEPT-950272 trial that appear to represent both local trauma related to the injection (bruising, erythema, and pain) and also events suggestive of a possible immune reaction (urticaria, pruritis, and rash). There were also two reports of “drug hypersensitivity”, six reports of “hypersensitivity”, and one report of angioedema.

Table 50. Treatment Emergent Adverse Events Leading to Withdrawal from the Amgen Metreleptin Obesity Program and the Metreleptin + Pramlintide Obesity Program

Preferred Term	Metreleptin	Placebo
	n (%)	n (%)
AMGEN LEPT-960176 (N=151)	**n=151**	**N/A**
Dyspepsia	1 (0.7)	N/A
Cough	1 (0.7)	N/A
Respiratory Disorder	1 (0.7)	N/A
Flushing	1 (0.7)	N/A
Lesion Skin	1 (0.7)	N/A
AMGEN LEPT-960240 (N=30)	**n=23**	**n=7**
Headache	1 (4.3)	0 (0.0)
Somnolence	1 (4.3)	0 (0.0)
Joint Stiffness	1 (4.3)	0 (0.0)
Micturition Frequency	1 (4.3)	0 (0.0)
AMGEN LEPT-970121 (N=124)	**n=82**	**n=42**
Asthenia	1 (1.0)	0 (0.0)
Edema Peripheral	1 (1.0)	0 (0.0)
Fever	2 (2.0)	0 (0.0)
Rigors	1 (1.0)	0 (0.0)
Nausea	1 (1.0)	0 (0.0)
Pruritus	3 (4.0)	0 (0.0)
Rash	3 (4.0)	0 (0.0)
Rash Erythematous	1 (1.0)	0 (0.0)
Urticaria	1 (1.0)	0 (0.0)
AMGEN LEPT-970211 (N=6)	**n=5**	**n=1**
Fever	1 (20.0)	0 (0.0)
Headache	1 (20.0)	0 (0.0)
Meningitis	1 (20.0)	0 (0.0)
Device Complication	1 (20.0)	0 (0.0)
AMGEN LEPT-950272 (N=250)	**n=177**	**n=73**
Dermatitis Contact	1 (0.6)	0 (0.0)
Diarrhea	1 (0.6)	0 (0.0)
Erythema	1 (0.6)	0 (0.0)
Fever	1 (0.6)	0 (0.0)
Headache	1 (0.6)	0 (0.0)
Injection Site Ecchymosis	1 (0.6)	0 (0.0)
Injection Site Edema	2 (1.1)	0 (0.0)
Injection Site Erythema	9 (5.1)	0 (0.0)
Injection Site Inflammation	7 (4.0)	0 (0.0)
Injection Site Mass	7 (4.0)	0 (0.0)
Injection Site Pain	3 (1.7)	0 (0.0)
Injection Site Pruritis	5 (2.8)	0 (0.0)
Injection Site Rash	1 (0.6)	0 (0.0)
Injection Site Reaction	1 (0.6)	0 (0.0)
Injection Site Urticaria	1 (0.6)	0 (0.0)
Insomnia	1 (0.6)	0 (0.0)
Malaise	1 (0.6)	0 (0.0)
Palpitation	1 (0.6)	0 (0.0)
Paresthesia	1 (0.6)	0 (0.0)
Pruritis	2 (1.1)	0 (0.0)
Urticaria	1 (0.6)	0 (0.0)
Vomiting	1 (0.6)	0 (0.0)

Preferred Term	Metreleptin	Placebo
	n (%)	n (%)
DFA101 (N=83)	**n=83**	**N/A**
Myocardial Infarction	1 (1.2)	N/A
Nausea	1 (1.2)	N/A
Injection Site Pruritus	1 (1.2)	N/A
Injection Site Scar	1 (1.2)	N/A
Drug Hypersensitivity	1 (1.2)	N/A
Hypersensitivity	3 (3.6)	N/A
DFA102 (N=531)	**n=456**	**n=75**
Abdominal Pain Upper	1 (0.2)	0 (0.0)
Nausea	3 (0.7)	0 (0.0)
Injection Site Erythema	1 (0.2)	0 (0.0)
Injection Site Nodule	1 (0.2)	0 (0.0)
Injection Site Pruritus	1 (0.2)	0 (0.0)
Injection Site Rash	1 (0.2)	0 (0.0)
Injection Site Urticaria	4 (0.9)	0 (0.0)
Drug Hypersensitivity	1 (0.2)	0 (0.0)
Hypersensitivity	2 (0.4)	0 (0.0)
Kidney Infection	1 (0.2)	0 (0.0)
Blood Creatine Phosphokinase Increased	1 (0.2)	2 (2.7)
Blood Pressure Increased	0 (0.0)	1 (1.3)
Papillary Thyroid Cancer	1 (0.2)	0 (0.0)
Menorrhagia	1 (0.2)	0 (0.0)
Angioedema	1 (0.2)	0 (0.0)
Generalised Erythema	1 (0.2)	0 (0.0)
Urticaria	2 (0.4)	0 (0.0)
DFA102E (N=273)	**n=242**	**n=31**
Abdominal Pain	1 (0.4)	0 (0.0)
Injection Site Nodule	1 (0.4)	0 (0.0)
Hypersensitivity	1 (0.4)	0 (0.0)
DFA104 (N=72)	**n=36**	**n=36**
Coronary Artery Disease	1 (2.8)	0 (0.0)

N/A=not applicable
Note: No adverse events leading to withdrawal were reported for Amgen Studies LEPT-970161, LEPT-980219, LEPT-980225, LEPT-980145, LEPT-980298, and DFA103.
For Amgen studies multiple events may have been recorded for a subject as an adverse event leading to withdrawal whereas for the pramlintide+metreleptin studies only the primary event which led to the withdrawal was recorded.

Source: Response to FDA Request for Information Dated 24-May-2013, Attachment 1 Table 2

7.3.4 Significant Adverse Events

I believe that two safety concerns can be considered “significant”: malignancy and immunogenicity.

Leptin, its implication in the development of cancer, and adverse events of malignancies seen in the clinical trials (lipodystrophy and non-lipodystrophy programs) are discussed in Section 7.6.1, Human Carcinogenicity.

The immunogenicity of metreleptin is discussed in Section 7.4.6, Immunogenicity.

7.3.5 Submission Specific Primary Safety Concerns

Hypoglycemia

Hypoglycemia of either mild or moderate intensity was the most frequent adverse event in the lipodystrophy trials, reported in eight (11.1%) of 72 patients (nine events) in the NIH trials and in seven (25.0%) of 28 patients (13 events: 11 mild, one moderate, one severe) in trial FHA101.

In the NIH trials, hypoglycemia was reported only in those patients receiving concomitant insulin therapy (short-acting, long-acting, or Humulin-R, U-500) with or without oral anti-hyperglycemic agents (including sulfonylureas, metformin, and thiazolidinediones). No severe hypoglycemia events (e.g., requiring the assistance of another individual) were reported. Two hypoglycemia events occurred in Patient 90102. The patient's insulin regimen (ultralente and regular insulin) was discontinued after the second event; no events of hypoglycemia were reported for this patient after discontinuation of insulin.

In trial FHA101, one patient (677001) experienced a severe event of hypoglycemia that required assistance from another person and was considered a serious adverse event although the patient was not taken to the hospital (see the narrative in Section 7.3.2, Serious Adverse Events). One patient (648020) had five events of hypoglycemia reported.§§§§§§§§ Most events of hypoglycemia occurred in patients who were receiving concomitant insulin therapy or a sulfonylurea with or without other oral antihyperglycemic agents, except Patient 648022 who experienced the event of hypoglycemia while on metformin approximately five months after starting metreleptin and had been on levemir and humalog insulins until about 3-4 months before the event. Concomitant diabetes therapy in these patients included rapid-acting, short-acting and long-acting insulins, U-500 insulin and insulin mixtures, as well as oral agents including sulfonylureas, metformin, and gliptins.

At the four-month safety update, 10 (11.1%) of 90 patients in the NIH trial reported hypoglycemia (two new events since the previous data cutoff). The two new events of hypoglycemia in two patients (one "occasional" and the other "intermittent" hypoglycemia) were both ongoing at the time of the four-month safety update data cutoff. These events were considered by the investigator as mild in intensity. Both patients were receiving concomitant insulin at the time of the events.

At the four-month safety update, 12 of 35 (34.3%) patients in the trial FHA101 reported hypoglycemia (including five patients with 12 new events). Seven of these events were considered mild, four moderate and one severe. This severe event was considered by the investigator as serious (see the narrative in Section 7.3.2, Serious Adverse Events;

§§§§§§§§ This was a 58 yo F with FPL, who at baseline had an HbA1c of 8.1% and FPG of 61 mg/dL.

this occurred in Patient 648005, who had a total of three hypoglycemia adverse events[*********] reported in the four-month safety update). All of the hypoglycemia events occurred in patients who were receiving concomitant insulin therapy or a sulfonylurea with or without other oral antihyperglycemic agents. Concomitant diabetes therapy in these patients included rapid-acting, short-acting and long-acting insulins, U-500 insulin and insulin mixtures, as well as oral agents including sulfonylureas, metformin, and gliptins.

In the five Amgen obesity trials in the ISS, hypoglycemia was reported overall in 3.6% and 1.4% in metreleptin- and placebo-treated patients, respectively. Hypoglycemia was reported only in the two trials in obese patients with type 2 diabetes (LEPT-970171 and LEPT-970188); in these trials the incidence in metreleptin-treated patients was 14.3% and in placebo-treated patients, 5.0%. Patients in LEPT-970171 were on stable doses of either glipizide or glyburide prior to the study, but dose adjustment was permitted during the study to minimize hypoglycemia, [†††††††††] whereas patients in LEPT-970188 had diet-treated diabetes and were prohibited from taking oral hypoglycemic agents within 12 weeks of screening. No hypoglycemia adverse events were reported in obese patients without diabetes.

A total of 11 metreleptin-treated patients reported hypoglycemic events compared to eight placebo-treated patients in the Amgen trials not included in the ISS and the metreleptin + pramlintide for obesity clinical program. All hypoglycemic events occurred in placebo-controlled trials. None of these events was considered serious and none led to study withdrawal. Events occurred with similar incidence in metreleptin- and placebo-treated patients.

Pancreatitis

Patients with lipodystrophy are predisposed to acute pancreatitis, due to marked hypertriglyceridemia (often defined as TG greater than 1000 mg/dL). In the NIH trials, 16 (22.2%) patients had a medical history of pancreatitis and 4 (5.6%) patients had a history of recurrent pancreatitis. Although some patients treated with metreleptin appeared to have significant improvement in TG concentrations, many patients continued to have high or fluctuating TGs, and adverse events of pancreatitis were seen in the lipodystrophy trials. As there was no control group, and the trials were not powered to detect either an improvement or worsening in pancreatitis, it is difficult to know the impact of metreleptin on pancreatitis in a patient population predisposed to this adverse event. The sponsor has proposed that patients who developed pancreatitis were non-compliant or they discontinued or interrupted metreleptin too rapidly with subsequent rebound in serum TG.

[*********] This patient also had a witnessed transient 'loss of consciousness' event reported, although without a blood sugar reported and no further information provided.
[†††††††††] Sulfonylurea use between groups was not described.

Reviewer comment: While it is reasonable to conclude that lack of metabolic control (whether it is due to noncompliance with metreleptin, diet, or concomitant medications) might put a patient with severe hypertriglyceridemia at risk for pancreatitis, I could not confirm a causal association between noncompliance and/or abrupt discontinuation and pancreatitis in all cases. Please see the narratives below.

In the NIH trials, 20 (27.8%) of the 72 patients had a medical history of pancreatitis (16, 22.2%) or recurrent pancreatitis (4, 5.6%), and in FHA101, two (8%) of 25 patients with medical history captured had a history of pancreatitis.

The following table summarizes pancreatitis serious adverse events and non-serious adverse events for the lipodystrophy trials; narratives of pancreatitis serious adverse events follow. Of note, each patient who developed pancreatitis in the trial had a history of pancreatitis.

Table 51. Adverse Events of Pancreatitis in the Lipodystrophy Trials

Patient ID Age / Sex / Type	Relevant Medical History / Baseline TG	Verbatim Term / SAE?	Time to Onset (Days)
90101 17 / F / AGL	Pancreatitis Hypertriglyceridemia TG 7420 mg/dL Xanthoma	Recurrent pancreatitis / N	268
		Pancreatitis / Y	4084
90109 13 / F / AGL	Pancreatitis Hypertriglyceridemia TG 2984 mg/dL Xanthoma	Pancreatitis attack / Y	168
90121 32 / F / FPL	Pancreatitis Hypertriglyceridemia TG 2324 mg/dL Xanthoma Chronic abdominal pain	Acute exacerbation of pancreatitis / Y	43
90125 15 / F / CGL	Pancreatitis TG 1669 mg/dL	Bout of pancreatitis / Y	104
90138 34 / F / FPL	Pancreatitis Hypertriglyceridemia TG 359 mg/dL	Pancreatitis / Y	876
648001 9 / F / AGL	Acute pancreatitis High triglycerides TG 10623 mg/dL	Acute pancreatitis / Y	191
		Pancreatitis / Y	1205

Source: Clinical Safety Update, Table 43; Four-month safety update, Attachment 1

Serious Adverse Events of Pancreatitis

Serious adverse events of pancreatitis are described in more detail here:

- NIH Patient 90101: At study entry (02 Aug 2000), this was a 17-year-old white female with a history of AGL. Other relevant medical history included hypertriglyceridemia, insulin resistance, recurrent pancreatitis, diabetes mellitus, diabetic nephropathy, hepatomegaly, abdominal pain, nausea, vomiting, inflamed bowel, asthma, scoliosis, kidney enlargement, and hepatic steatosis. On (b) (6) (b) (6), after 11 years of treatment, the patient was taken to the emergency room for nausea, vomiting, and abdominal pain, and was admitted the following morning. Laboratory tests showed a lipase greater than 5000, TG 300, and blood glucose values of 350 and 237 (units and reference ranges not specified). She was diagnosed with pancreatitis and treated with bowel rest, nasogastric drainage, intravenous fluids, hydromorphone, and SC insulin. She was also felt to have an ileus. The patient was not sure what triggered the pancreatitis as "her triglycerides had been good lately," and she did not alter her diet; she thought that it may have been related to vomiting associated with her recent menstrual period. There was no indication of non-compliance in terms of the pancreatitis event. An upper gastrointestinal study (unspecified) was performed on (b) (6) (results not available); superior mesenteric artery syndrome was diagnosed and thought to be the cause of some of the patient's symptoms. The patient underwent duodenojejunostomy on (b) (6) and recovered uneventfully. The superior mesenteric artery syndrome and pancreatitis were reported resolved on 17 Oct 2011. Metreleptin treatment was continued through the hospital course and the patient continued participation in the study as of the data cutoff date of 11 Jan 2013.

- NIH Patient 90109: At study entry ((b) (6)), this was a 13-year-old white female with a seven-year history of AGL. Other relevant past medical history at study entry included episodes of pancreatitis (most recent episode Jun 2001) and hypertriglyceridemia (6000-10000 mg/dL prior to metreleptin therapy and 3000-6000 mg/dL after starting metreleptin therapy). At baseline, the patient's TG was 2984 mg/dL with subsequent values after starting metreleptin treatment of 6910 mg/dL on 17 Oct 2001, 2842 mg/dL on 26 Nov 2001, and 5795 mg/dL on 28 Jan 2002. On (b) (6) (b) (6) Day 169 of treatment with metreleptin, the patient experienced the sudden onset of abdominal pain, nausea, and vomiting. The amylase concentration was 377 U/L (normal range: 25-125 U/L), and a presumptive diagnosis of pancreatitis was made. The patient was admitted for NPO status and IV fluid therapy, and was discharged on (b) (6). The event of pancreatitis was considered resolved after approximately one month on 28 Mar 2002. The patient continued participation in the study and receiving metreleptin treatment until she experienced a serious adverse event of hypoalbuminemia, proteinuria, and worsening liver disorder, after which she was withdrawn from the trial. She died approximately nine months later (see description in Section 7.3.1, Deaths).

Reviewer comment: Note that despite the report of TG values 6000-10,000 mg/dL prior to starting metreleptin, the patient's baseline TG value was recorded as 2984 mg/dL (suggesting that TG concentrations in some patients are very variable, and may be influenced by a number of factors, including diet). She continued to have very high TG values after metreleptin therapy, even during times of reported compliance with metreleptin therapy.

- NIH Patient 90121: At study entry ((b) (6)), this was a 32-year-old white female with FPL. Other relevant past medical history at study entry included history of multiple episodes of pancreatitis (further details not available), chronic abdominal pain, hypercholesterolemia, hypertriglyceridemia, steatohepatitis, and diabetes. At baseline, TG was 2324 mg/dL. On (b) (6), Day 44 of treatment with metreleptin, the patient was hospitalized with pancreatitis. Further details regarding this event of pancreatitis are not available. The event of pancreatitis resolved after 47 days on 01 May 2003. TG at the Month 4 visit (11 Jun 2003) was 530 mg/dL. The decision was made on 31 Aug 2004 to withdraw the patient from the trial as the investigator questioned her compliance with taking study medication. Metreleptin was tapered over the next week, and the patient took her last dose of study medication on 31 Aug 2004.

Reviewer comment: Of note, the patient's Month 8 TG was 752 mg/dL and the Month 12 TG was 1825 mg/dL. According to the information available, fenofibrate and omega-3 fatty acids were started at or before the Month 4 visit.

- NIH Patient 90125: This pancreatitis event was discussed above in Section 7.3.1, Deaths.

Reviewer comment: Patient compliance was questioned in this case; however, it is unknown whether the pancreatitis even can be ascribed to the patient's TGs being high because she was not taking metreleptin, or whether the drug was stopped without a taper and her TGs rapidly increased (as proposed by the investigator). Her baseline TG value was 1669 mg/dL, but there are not any additional follow-up values available.

- NIH Patient 90138: At study entry ((b) (6)), this was a 34-year-old female with FPL. Relevant medical history at study entry included pancreatitis. The patient presented with cold/flu-like symptoms for several days with nausea, vomiting, and diarrhea. On (b) (6), Day 870 of metreleptin treatment, she was hospitalized with a presumptive diagnosis of colitis. The hospital physician stopped metreleptin therapy on (b) (6) without consulting the study investigators. On (b) (6) (b) (6), it was noted that amylase and lipase levels had dramatically risen (values unavailable) from baseline at time of hospitalization on (b) (6). The patient subsequently developed pancreatitis. Further details about the pancreatitis are not

available. Metreleptin therapy was restarted on [redacted] and the patient was discharged from the hospital on [redacted]. The events of colitis and pancreatitis resolved after approximately seven days, and the patient had no further episodes of pancreatitis. The event of pancreatitis was felt by the investigator to have occurred due to the abrupt withdrawal of metreleptin.

Reviewer comment: No details were provided about this hospitalization, so it is difficult to comment on the assertion that pancreatitis was due to abrupt metreleptin withdrawal (i.e., it is not clear if the diagnosis of colitis was in fact early pancreatitis, what other medications may have been stopped at the time of hospitalization, or what the TG values were at the time of diagnosis). The patient's available TG values were as follows: baseline: 359 mg/dL, Month 4: 405 mg/dL, Month 12: 295 mg/dL, Year 2 (last available value prior to hospitalization, [redacted]): 873 mg/dL, unscheduled visit May 2011 963 mg/dL. Compliance was not recorded for this patient. She was on fenofibrate at baseline, which continued throughout the trial. Fish oil was added to her regimen at or before the Month 4 visit.

- NIH Patient 90180 (enrolled subsequent to the July 2011 data cut; these are adverse events of "abdominal pain", not "pancreatitis"): At study entry ([redacted]), this was a 28-year-old white female with FPL. Other relevant medical history included hypertension, chronic pancreatitis (usually in conjunction with hypertriglyceridemia of 500 to 14000 mg/dL), extreme insulin resistance with type 2 diabetes, diabetic ketoacidosis, duodenitis, gastroesophageal reflux disease, constipation, polycystic ovary syndrome, menstrual irregularities, anemia, chronic pain disorder (with chronic opioid use), and prior cholecystectomy. Prior to metreleptin therapy, she reportedly had attacks requiring hospitalization every 3 to 4 weeks. She was admitted to the hospital on [redacted] with similar symptoms of abdominal pain and nausea. On [redacted], laboratory tests showed TG of 2300 mg/dL, and normal amylase and lipase (results not provided). A consultant noted that the patient struggled with binge eating disorder. Her diet was advanced and she was able to tolerate a regular diet with some mild abdominal cramps and slight nausea. She was discharged from the hospital on [redacted], with TG of 405 mg/dL and lipase 73 U/L on the day of discharge. On [redacted], Day 108 of treatment with metreleptin, the patient was admitted to the hospital with abdominal pain, poorly controlled diabetes, and electrolyte and acid-base disturbances. She stated that she had been feeling more hungry and eating more than usual for approximately two weeks. On [redacted], she missed her morning dose of metreleptin and did not realize it until taking her evening dose; she also stated that her insulin pump ran out of medication around 4 p.m. She ate dinner, and several hours later began having severe, sharp, epigastric pain, radiating to the back, associated with abdominal bloating and regurgitation of food, but no frank emesis. Upon admission, her amylase and lipase were within normal limits; TG (fasting) one day after being admitted was 8861 mg/dL and

glucose 432 mg/dL. A CT scan of the abdomen and pelvis with contrast revealed a diffuse fatty liver; no evidence of acute pancreatitis; and a collapsing right corpus luteum with a small amount of free pelvic fluid. The patient received ondansetron and promethazine. Metreleptin therapy was continued. Her condition improved and at discharge, TG was 614 mg/dL. On (b) (6), Day 197 of treatment with metreleptin, the patient was hospitalized for abdominal pain and nausea. She had not previously missed any metreleptin doses or eaten any large and/or fatty meals. Fasting laboratory tests showed TG of 5881 mg/dL and lipase 82 U/L. The patient received ondansetron, promethazine, and hydromorphone. Metreleptin therapy was continued. Further details of the patient's hospital course were not available at the time of this report. The event of abdominal pain resolved on 14 Dec 2012. The patient continued participation in the study as of the data cutoff date of 11 Jan 2013.

Reviewer comment: The three adverse events reported for this patient were named "abdominal pain"; however, they occurred in conjunction with elevated TGs in a patient who has a history of similar attacks of low amylase and lipase and high TGs. These cases are of relevance, because in at least one instance, they occurred when the patient was purportedly compliant with her metreleptin treatment.

- FHA101 Patient 648001 (two events): At study entry (b) (6)), this was a 9-year-old black female with juvenile dermatomyositis and AGL diagnosed in 2007. Relevant medical history at study entry included history of acute pancreatitis (two episodes: one in 2008 and one in 2009), insulin resistance, type 1 diabetes mellitus, high triglycerides, increased liver size and fatty infiltration of liver, minimal proteinuria, history of nausea and vomiting, and heartburn. At baseline, the patient's TG was 10623 mg/dL. Following metreleptin treatment, the TG decreased to 1059 mg/dL at Month 3 (29 Jun 2009) and increased to 3901 mg/dL at Month 6 (22 Sep 2009). On (b) (6) day 192 of metreleptin treatment, the patient experienced nausea, vomiting, and pain in her flanks and lower abdomen. The patient developed a fever and poor appetite two days later. On admission to the hospital, lipase was 303 IU/L (normal 5-50 IU/L) and amylase was 91 (normal 30-100 U/L). The blood sample was noted to be lipemic but TG was not reported. Results of the CT scan were consistent with pancreatitis. The patient was discharged on (b) (6). Study medication was stopped during hospitalization, but restarted upon discharge. Follow-up TG values were: 2743 mg/dL on 04 Nov 2009, 4594 mg/dL at Month 9, 4296 mg/dL at Month 10, 3566 mg/dL at Month 11, and 140 mg/dL at Month 12. On (b) (6), approximately 3.3 years after initiating metreleptin therapy, she experienced worsening migraine with vomiting and was taken to the emergency room. Her blood glucose was 179 mg/dL prior to going the ER. Upon arrival at the ER, she complained of sharp, diffuse abdominal pain, and was febrile with a temperature of 38.6°C and heart rate 140-150 bpm. Laboratory tests showed a lipase level of 4622 U/L, and a blood glucose of 542, pH 7.21, and anion gap 27. On admission to the pediatric ICU, she was found to be in mild DKA with + urine

ketones, TG 18110 mg/dL, lipase 1710 U/L, amylase 701 IU/, and creatine phosphokinase 428 IU/L (NR 26-180). Her CT scan was interpreted at the hospital as showing pancreatic enlargement. Of note, at her most recent scheduled visit prior to this hospitalization on (b) (6) her TG was 1541 mg/dL. Plasmapheresis was performed, with TG decreasing to 4022 mg/dL and then 3071 mg/dL. She experienced abdominal pain and distention. An abdominal x-ray on (b) (6) was consistent with an ileus. On (b) (6), the patient's amylase was 201 IU/L, lipase 427 U/L, and TG 3169 and 1452 mg/dL. Metreleptin therapy was restarted on (b) (6). On (b) (6), the patient's TG was 602 mg/dL and lipase was 151 U/L. The patient was discharged on (b) (6). The patient continued participation in the study.

Reviewer comment: Compliance with metreleptin was not reported in the narrative, although according to additional information provided by the sponsor, the PI believed there was a compliance issue with metreleptin, insulin, and diet. It is noted that she was started on omega-3 fatty acids in addition to fenofibrate and simvastatin at Month 6.

In addition to pancreatitis events in the lipodystrophy trials, there was one event of pancreatitis on Day 85 in a patient with obesity treated with metreleptin in the Amgen trial LEPT-970171. This case was discussed above in Section, 7.3.2, Serious Adverse Events. No pancreatitis adverse events were reported in the 10 Amgen trials not included in the ISS or the metreleptin + pramlintide for obesity clinical program.

In the compassionate use programs and investigator-initiated trials, five pancreatitis-related serious adverse events were reported, all in patients with lipodystrophy. Four out of the five patients had pre-existing hypertriglyceridemia and one patient had a history of gallstones. Two of the cases were reportedly associated with metreleptin non-compliance.

Table 52. Individual Patient Data for Patients with Pancreatitis-Related Serious Adverse Events: Metreleptin in Compassionate-Use and Investigator-Initiated Trials

Compassionate Use Trials (Named Patient Program)					
Indication	Study ID Age / Sex / Type	Relevant Medical History	SAE	Time to Onset	Relevant Comments
Lipodystrophy	NPP-Germany 24 / F / partial lipodystrophy	Diabetes mellitus, hypertriglyceridemia, pancreatitis (4 events prior to start of metreleptin treatment)	Pancreatitis	480 days	Metreleptin continued at an increased dose to assist with control of pancreatitis
Lipodystrophy	NPP-United Kingdom 55 / F / partial lipodystrophy	Hepatic steatosis, mildly elevated liver enzymes, fatty liver, gallstones, cholecystectomy	Pancreatitis	6 days	The reporting physician requested the event term be updated to abdominal pain cause unknown, possibly mild pancreatitis.
Investigator-Initiated Trials					
Lipodystrophy	20020368 33 / F / not reported	Hypertriglyceridemia, diabetes, bipolar disorder	Pancreatitis acute	Approximately 8 months	Ultrasound showed enlarged fatty liver, normal gallbladder, poorly visualized pancreas. Diagnosed with possible acute pancreatitis.
Lipodystrophy	20020701 (and extension study) 18 / F / CGL	Hypertriglyceridemia, diabetes, treatment non-compliance, Bell's palsy	2 events of pancreatitis	Approximately 15 months and 19 months	Patient was treatment non-compliant, poorly controlled diabetes, HbA1c 11.2%, glucose 352 mg/dL, diabetic kketoacidosis on admission, TG 5250 mg/dL

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-10

Liver-Related Adverse Events

Patients with lipodystrophy who have undergone liver biopsy have been described to fall within the spectrum of non-alcoholic fatty liver disease (NAFLD), from none to inflammation and fibrosis (including cirrhosis), as well as having other liver diseases such as autoimmune hepatitis. Historically, cirrhosis has been reported in about one-fifth of AGL patients as a late sequela of hepatic steatosis or autoimmune hepatitis.[2] In CGL, hepatomegaly from fatty liver is reported to be almost universal and may lead to cirrhosis.[2]

In the NIH trial, 32 (44%) patients had a medical history of steatohepatitis and 14 (19.4%) patients had a history of hepatic steatosis. Six (8.3%) patients had cirrhosis (three of whom also had steatohepatitis), and four (5.6%) patients had hepatic fibrosis (one also with steatohepatitis, two also with autoimmune hepatitis, one also with hepatic steatosis). Six percent of patients with AGL and 16% of patients with CGL had cirrhosis at baseline (cirrhosis was not reported in patients with partial lipodystrophy). In the FHA101 trial, 19 (76%) of 25 patients (with medical history captured) had a medical history of hepatic steatosis, and one (4%) of 25 patients had a medical history of autoimmune hepatitis.

Table 53. Liver-Related Adverse Events in the Lipodystrophy Trials

Patient ID Age / Sex / Type	Relevant Medical History (Baseline AST / ALT)	Verbatim Term / SAE?	Time to Onset (Days)
90103 27 / F / AGL	Autoimmune hepatitis, liver fibrosis (AST 57, ALT 128)	Increased liver enzymes / Y	481
90107 42 / F / FPL	Hepatomegaly, focal glomerulonephritis (AST 28, ALT 28)	Steatohepatitis / N	6
90109 13 / F / AGL	Nonalcoholic steatohepatitis, bridging fibrosis (AST 85, ALT 79)	Chronic inflammatory hepatitis / N	382
		Worsening of liver disease / Y	422
90110 8 / F / AGL	Autoimmune hepatitis, mild portal fibrosis, fatty liver (AST 38-39, ALT 53-56)	Elevated ALT level of 317 U/L / Y	34
		Worsening autoimmune hepatitis / N	2443
90158 18 / F / AGL	Severe liver disease with cirrhosis (AST 142, ALT 105)	Hepatic encephalopathy / Y	344
		Progressive end stage liver disease / Y (fatal)	523
648004 30 / F / FPL	Fatty liver, increased LFTs (AST 21, ALT 14)	Elevated AST levels (AST 78, ALT 33) / N	443

648016 11 / M / AGL	Chronic active autoimmune hepatitis, history of elevated LFTs (AST 208, ALT 419)	Increased LFTs / N	9

Reviewer comment: Note that five out of seven cases occurred in patients with AGL, three of whom had known autoimmune hepatitis at baseline. Patients with AGL and autoimmune hepatitis may be at risk for exacerbation of autoimmune hepatitis with metreleptin.

The following table presents a categorical summary of patients who had increases in AST or ALT at least three, five, or 10 times the upper limit of normal (ULN) at least one time or at two or more consecutive visits. Notably all patients with categorical increases in transaminases had a diagnosis of chronic liver disease at baseline (typically steatohepatitis, cirrhosis, and/or autoimmune hepatitis) except for Patient 90142 who had a history of hepatomegaly and substantially elevated transaminases at baseline but without a specific diagnosis of liver disease. No patient met the criteria for 2X ULN for total bilirubin (therefore, no patient met the criteria for Hy's Law[‡‡‡‡‡‡‡‡‡]). One patient (90158) who had a medical history of severe liver disease with cirrhosis had a slightly elevated total bilirubin measurement at baseline (1.1 mg/dL) which increased to 1.7 mg/dL at Month 8. This patient died due to progressive end stage liver disease. See the narrative in Section 7.3.1, Deaths.

[‡‡‡‡‡‡‡‡‡] "Hy's Law": Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). See: *Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation.*

Table 54. Categorical Summary of AST and ALT Values, NIH Trials

Analyte Category	Generalized Lipodystrophy n (%) [RPY]	Partial Lipodystrophy n (%) [RPY]	All Patients n (%) [RPY]
AST (IU/L)			
N with at least 1 post-BL measurement	**46**	**22**	**68**
Post-BL ≥3 X ULN at least 1 time	9 (19.6) [0.048]	2 (9.1) [0.022]	11 (16.2) [0.040]
Post-BL ≥5 X ULN at least 1 time	6 (13.0) [0.032]	2 (9.1) [0.022]	8 (11.8) [0.029]
Post-BL ≥10 X ULN at least 1 time	2 (4.3) [0.010]	0 (0.0) [0.000]	2 (2.9) [0.007]
N with at least 2 post-BL measurements	**40**	**21**	**61**
Post-BL ≥3 X ULN at 2 or more consecutive visits	2 (5.0) [0.010]	1 (4.8) [0.011]	3 (4.9) [0.011]
Post-BL ≥5 X ULN at 2 or more consecutive visits	1 (2.5) [0.005]	1 (4.8) [0.011]	2 (3.3) [0.007]
Post-BL ≥10 X ULN at 2 or more consecutive visits	1 (2.5) [0.005]	0 (0.0) [0.000]	1 (1.6) [0.004]
ALT (IU/L)			
N with at least 1 post-BL measurement	**46**	**22**	**68**
Post-BL ≥3 X ULN at least 1 time	8 (17.4) [0.045]	5 (22.7) [0.065]	13 (19.1) [0.051]
Post-BL ≥5 X ULN at least 1 time	6 (13.0) [0.032]	2 (9.1) [0.023]	8 (11.8) [0.029]
Post-BL ≥10 X ULN at least 1 time	2 (4.3) [0.010]	1 (4.5) [0.011]	3 (4.4) [0.010]
N with at least 2 post-BL measurements	**40**	**21**	**61**
Post-BL ≥3 X ULN at 2 or more consecutive visits	2 (5.0) [0.010]	3 (14.3) [0.037]	5 (8.2) [0.018]
Post-BL ≥5 X ULN at 2 or more consecutive visits	2 (5.0) [0.010]	2 (9.5) [0.023]	4 (6.6) [0.014]
Post-BL ≥10 X ULN at 2 or more consecutive visits	0 (0.0) [0.000]	0 (0.0) [0.000]	0 (0.0) [0.000]

BL = baseline.
Notes: Increases are from baseline, which is defined as the last available value before the patient received the first injection of metreleptin.
- [RPY] = Rate per Patient Year, derived by dividing n by patient years of exposure. If a patient had the event, their exposure is truncated at the time of event.
- Normal ranges were not collected. For the purposes of this analysis, 34 IU/L was used as the upper limit of normal (ULN) for AST and 41 IU/L was used for ALT.
Source: Clinical Safety Update, Table

In the FHA101 trial, mean values for ALT and AST were slightly above the upper limit of normal for the overall population (N = 28) (ALT [mean ± SE] 54 ± 16 U/L, AST 39 ± 8 U/L). In those patients with elevated baseline values (n = 9 for ALT, n = 7 for AST), ALT decreased from 133 ± 56 to 41 ± 6, and AST from 91 ± 28 U/L to 36 ± 4 U/L at Month 6. These improvements were primarily driven by two patients with AGL: Patient 648016 with ALT decreasing from 419 to 89 U/L and AST from 208 to 36 U/L) at Month 6 (see the liver-related adverse event reported in this patient in the table above), and Patient 648022 with ALT decreasing from 259 to 19 U/L and AST from 145 to 20 U/L at Month 6. No patients in FHA101 had an increase in ALT or AST greater than 3X ULN, nor did any patient have a total bilirubin elevation greater than 2X ULN.

No liver-related adverse events were reported in metreleptin-treated patients across the five integrated obesity trials from the ISS: LEPT-970164, LEPT-970213, LEPT-980236, LEPT-970188, and LEPT-970171. In metreleptin-treated patients, mean changes from baseline to the last post-baseline assessment were -0.7 U/L versus -0.2 U/L for placebo for AST and -2.0 U/L versus -0.7 U/L for placebo for ALT. There was a slightly higher incidence (0.7% vs. 0.3%) for metreleptin-treated patients meeting ALT 3X ULN criteria compared to placebo. No patients (metreleptin or placebo) who met criteria for

increases in AST or ALT greater than 3X ULN had increases in total bilirubin greater than 2X ULN; therefore, there were no cases that met the criteria of Hy's Law.

In the Amgen trials not included in the ISS as well as the metreleptin + pramlintide for obesity clinical program, the following liver-related adverse events were reported (no further details were provided):

- One case of blood bilirubin increased in a metreleptin-treated patient
- Three cases of ALT increased in metreleptin-treated patients and one case in a placebo-treated patient
- Three cases of AST increased in metreleptin-treated patients and one case in a placebo-treated patient

Nephropathy

Lipodystrophy Trials

A high incidence of proteinuric nephropathies [e.g., membranoproliferative glomerulonephritis (MPGN) and focal segmental glomerulosclerosis (FSGS) as well as diabetic nephropathy] has been noted in patients with generalized lipodystrophy.[30] Acquired partial lipodystrophy is also associated with a higher frequency of MPGN.[2]

In the NIH trials, 24 (33%) patients, and in FHA101, seven (28%) patients had a medical history of proteinuria. Four (5.6%) patients in the NIH study had a medical history of glomerular disease (three with FSGS, two of whom also had proteinuria, and one with focal glomerulonephritis, also with proteinuria).

Adverse Events

The table below summarizes adverse events relevant to proteinuric nephropathies. Individual patient narratives for those events that were deemed serious can be found in Section 7.3.1, Deaths (Patient 90106) and Section 7.3.2, Nonfatal Serious Adverse Events (Patients 90107 and 90109[§§§§§§§§§]).

All of these events occurred in patients with a diagnosis or evidence of renal disease at baseline (proteinuria, glomerulonephritis, chronic renal failure). In FHA101, there were no events relevant to chronic renal disease reported in the 28 patients.

[§§§§§§§§§] Patient 90109 died of liver and renal failure 9 months after discontinuing metreleptin.

Table 55. Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to Chronic Renal Disease

Patient ID Age / Sex / Type	Relevant Medical History (Baseline 24-hr Urine Protein)	Verbatim Term	Time to Onset (Days)	SAE?
90106 35 / F / CGL	Proteinuria (2.8g/24h)	Proteinuria Kidney failure	65 3464	N Y - fatal
90107 42 / F / FPL	Focal glomerulonephritis, stage IV kidney failure, proteinuria (1.9g/24h)	End stage renal disease Right renal transplant	2519 (approx.) 2748	N Y
90109 13 / F / AGL	Proteinuria (2.7g/24h)	Membranoproliferative glomerulonephritis Worsening of proteinuria	441 422	N Y
90113 12 / F / CGL	Proteinuria (3.2g/24h)	Focal proliferative glomerular sclerosis	327 (approx.)	N
90114 35 / M / AGL	Chronic renal failure, proteinuria (2.5g/24h)	Membranoproliferative glomerulonephritis Worsening of proteinuria	270 270	N N[1]
90163 20 / F / CGL	Proteinuria (5.5g/24h)	Focal segmental glomerulosclerosis	136	N

[1] AE led to withdrawal, although the patient was subsequently enrolled in a compassionate use program in her country

Source: Clinical Safety Update, Table 42; Response to FDA Request for Information Dated 08-Oct-2013, Table 3

Proteinuria, Creatinine, and BUN

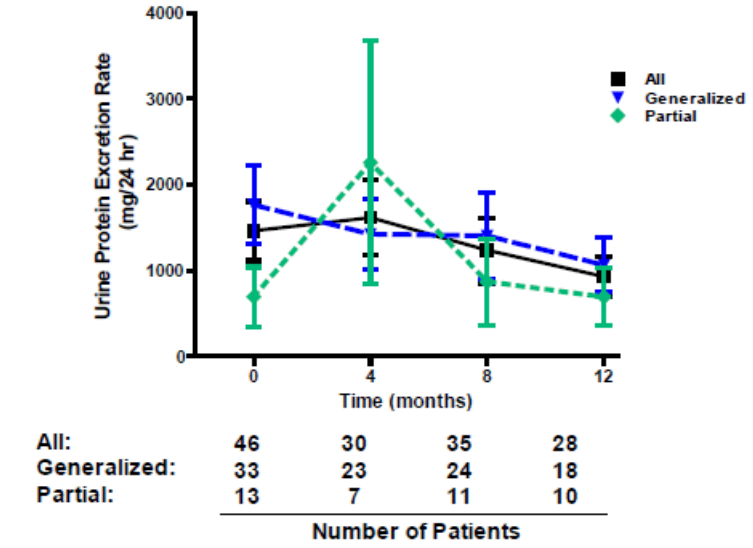
The NIH published[30] a 15-patient subset with generalized lipodystrophy evaluating proteinuric nephropathy in lipodystrophy patients.********** Of these 15 patients, it was reported that 11 (73%) had a reduction in proteinuria with treatment.

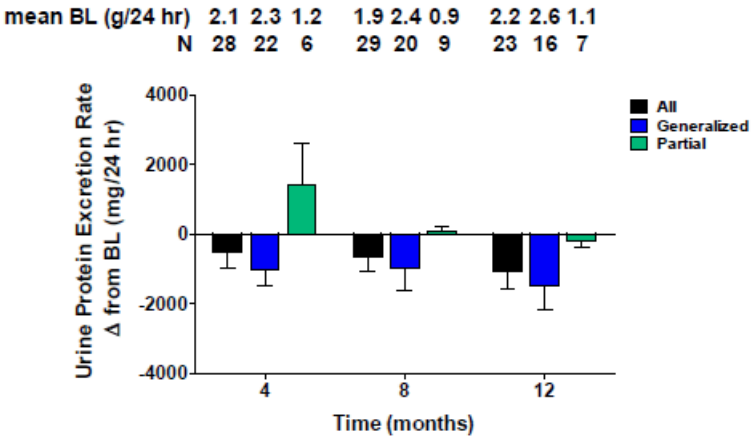
Reviewer comments: Note that two patients presented in the table above and also in the cited NIH publication, 90109 and 90114, had worsening of proteinuria. As described in other sections of this review, the contribution of metreleptin to the worsening of MPGN in these two patients cannot be excluded.

Mean changes from the available 24-hour urine protein measurements are presented in the figure below. The increase in the 24-hour urine protein was observed at Month 4 among patients with partial lipodystrophy was driven by the results in Patient 90107 who had an increase in 24-hr urine protein from 1.9 g/24 hr at baseline to 9.1 g/24 hr at Month 4, but eventually had a decreased 24-hr urine protein value with continued therapy.

********** Discrepancies were found between the publication and the BLA in baseline data (age and HbA1c) for patients 90105, 90106, 90122.

Figure 26. Mean (SE) 24-Hour Urine Protein Concentrations Over Time and Change From Baseline at Month 4, 8, and 12; NIH Trials





BL = baseline.

Source: Clinical Safety Update, Figure 1

Reviewer comments: Despite the sponsor's contention that metreleptin improves proteinuria, there appears to be a number of patients who developed worsening proteinuria or creatinine during the trial (see Table 56 below). It is plausible that the reduction in proteinuria reflects decreased glomerular hyperfiltration, but whether this is the result of a metreleptin-mediated metabolic process or other confounders (e.g., reductions in blood pressure, addition or intensification of relevant concomitant medications) cannot be determined. Furthermore, whether a treatment-associated reduction in proteinuria will translate into a benefit on

renal outcomes (i.e., irreversible loss of renal function and progression to ESRD) for the heterogeneous collection of renal diseases associated with lipodystrophy is unknown.

Limitations to the 24-hour urine protein assessments include: (1) urine creatinine was not reported, and (2) changes in concomitant medications (e.g., ACE-inhibitors, angiotensin receptor blockers) or blood pressure can affect proteinuria markedly; these factors were not controlled for in the trial.

The table below lists the patients who had an increase in creatinine of 0.3 mg/dL or greater at two or more consecutive visits (n = 5), and those who had an increase in 24-hr urine protein of 1 g or greater at least one time (n = 8) or at two or more consecutive visits (n = 2) or 2 g or greater at least one time (n = 5). No patients had an increase in 24-hr urine protein of 2 g or greater at two or more consecutive visits. With the exception of Patient 90112, who had a history of hypertension but without documented renal disease and no assessment of 24-hr urine protein at baseline, these patients had a history of renal disease or evidence of renal disease (i.e., proteinuria) at baseline.

Reviewer comment: Given the limitations to the medical history data, the proportion of patients who had baseline renal abnormalities and remained stable (or "improved") is unknown.

The most notable increases in creatinine occurred in four patients with renal disease at baseline: Patient 90102[††††††††††] with a history of focal segmental glomerulosclerosis and massive proteinuria at baseline; Patient 90106[‡‡‡‡‡‡‡‡‡‡] with proteinuria at baseline who eventually died of chronic renal failure; Patient 90107 with a history of glomerulonephritis, stage IV kidney failure[§§§§§§§§§§], and proteinuria at baseline; and Patient 90114 with proteinuria at baseline who was diagnosed with MPGN within the first eight months of treatment and withdrawn due to worsening proteinuria (see the

[††††††††††] The increases in creatinine and proteinuria in Patient 90102 were not captured as adverse events. This case is described further in an NIH publication[30] as follows: *Patient [90102] is a 17-yr-old female with CGL. She had a baseline urinary protein excretion of 11 g/24 h and a creatinine clearance of 73 ml/min. She was known to have proteinuria since age 11 yr, and a kidney biopsy done 2 yr before initiating leptin therapy revealed focal segmental glomerulosclerosis (FSGS). She was treated with leptin over an 18-month period during which she had a slow, but progressive, deterioration of renal function. There was an initial fall in urinary protein excretion that was not sustained. Leptin therapy was discontinued after 30 months as she approached end-stage renal disease.*

[‡‡‡‡‡‡‡‡‡‡] This patient initiated metreleptin treatment on 08 Sep 2000 but experienced an adverse event on the second day of treatment, and metreleptin was discontinued. She re-initiated metreleptin on 19 Sep 2000 but again discontinued one day later after she experienced another adverse event. Metreleptin was restarted on 15 Nov 2000, which was used as her modified first dose date for efficacy analyses. True baseline labs (prior to the first dose date on 08 Sep 2000) were not provided in the BLA, but the sponsor verified that a true baseline value for 24-hr urine protein is available for this patient (dated 07 Sep 2000): 2.8 g/24 hr (note the discrepancy between this value and the table below).

[§§§§§§§§§§] As reported in the table below; although it is noted that the patient's baseline creatinine was 1.6 mg/dL, which is consistent with an eGFR of ~40 mL/min (stage 3 CKD).

narrative for this patient's adverse event in Section 7.3.3, Dropouts and/or Discontinuations).

Table 56. Individual Patient Listing of Creatinine and 24-hr Urine Protein Increases Meeting Categorical Criteria (NIH Trial)

Patient ID / Demog	Relevant Medical History	Serum Creatinine (mg/dL)		24-hr Urine Protein (g/24 hr)			Summary of Post-Baseline 24-hr Urine Protein Values
		Incr ≥0.3 at least 2 times	Baseline to Last Available	Incr ≥1 g/24hr at least once	Incr ≥1 g/24 hr at least 2 times	Incr ≥2 g/24hr at least once	
90102 17 yr F, CGL	Focal segmental glomerulosclerosis, proteinuria (>11 g/24 hr)	X	1.4 to 2.9 (Month 16)	X		X	Proteinuria decreased to 3.3 g (Month 16), increased to >11 and >15 g (Year 2)
90106[1] 35 yr F, CGL	Proteinuria (2.6 g/24 hr)		0.7 to 2.8 (Year 9)				Proteinuria decreased to 616 mg (Month 10) and increased back to 2.3 g (Year 9)
90107 42 yr F, FPL	Focal glomerulonephritis, stage IV kidney failure, proteinuria (1.9 g/24 hr)	X	1.6 to 4.7 (Year 6), 0.9 after renal transplant	X		X	Proteinuria fluctuated (min 256 mg prior to renal transplant, max 9.1 g, final 161 mg)
90109 13 yr F, AGL	Proteinuria (2.7 g/24 hr)		0.3 to 0.5 (Month 16), max 0.6	X		X	Proteinuria decreased to 1.2 g, increased to 20 g final visit (SAE)
90110[1] 8 yr F, AGL	Mild proteinuria (390 mg to 1.5 g/24 hr) Kawasaki's disease		0.6 to 0.59 (Year 7), max 0.95	X			Proteinuria decreased to ~200 mg (Year 3)
90111 13 yr M, CGL	Proteinuria (252 mg/24 hr)	X	0.6 to 0.95 (Year 8), max 1.11				Proteinuria fluctuated (min 84 mg, max 567 mg, final 272 mg)
90112 64 yr F, FPL	Hypertension, baseline 24-hr urine protein not available	X	0.7 to 1.17 (Year 9), max 1.47				24-hr urine protein 95 mg (Month 30) and 206 mg (Year 7)
90113 12 yr F, CGL	Proteinuria (3.2 g/24 hr)		0.3 to 0.46 (Year 6), max 0.5	X		X	Proteinuria fluctuated (min 1 g, max 5.7 g, final 3.6 g)
90114 35 yr M, AGL	Chronic renal failure, proteinuria (2.45 g/24 hr)	X	1 to 2.2 (Month 8)	X	X	X	Proteinuria increased to 4.1 g (Month 4) and 8.9 g (Month 8)
90132 18 yr F, APL	Focal segmental glomerulonephritis, nephropathy, proteinuria (4.5 g/24hr)		0.2 to 0.3 (Year 1)	X	X		Proteinuria increased to 6 g (Month 4), decreased to 3 g (Year 1)
90137 13 yr F, CGL	Proteinuria (457 mg/24 hr), hypertension		0.5 to 0.69 (Year 4), max 0.8	X			Proteinuria increased to 1.9 g (Year 1), decreased to 1.2 g (Year 2)

Incr = increase; Yr = years; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.
[1] Modified first dose date due to on and off therapy.
Source: Clinical Safety Update, Table 26

One additional event of proteinuria was reported after the data cutoff for the BLA submission. Patient 90134, a 9-year-old male at study entry with CGL, experienced

worsening proteinuria approximately 5.5 years after initiating metreleptin treatment. The patient had a medical history of proteinuria (baseline 24-h urine protein 175.7 mg). At the time of the event, 24-h urine protein increased to 723.5 mg. At the final visit (at the time of data cutoff), 24-h urine protein had decreased slightly to 587.3 mg. The event was ongoing as of the 11 Jan 2013 data cutoff and was being treated with ramipril.

Although the evaluation is limited due to the fact that the sample size changes over time, there are potential renal function changes over time in this population, as well as no comparator group available, descriptive statistics of mean changes in BUN and creatinine by visit are presented below.

Reviewer comment: Mean values of BUN and creatinine were all well within normal, although a small increase in creatinine was seen over time, of unknown significance (note that there are only 2-3 patients' data available after Year 7).

Table 57. BUN Values and Change from Baseline by Visit

Parameter/Visit	n	Mean (SD)	SE	Median	Min	Max
BUN (mg/dL)						
Baseline [1]	72	12.26 (5.874)	0.692	11.00	2.0	38.0
Month 4	46	11.96 (5.573)	0.822	12.00	1.2	35.0
Month 8	54	12.04 (6.025)	0.820	11.00	2.0	32.0
Year 1	52	12.02 (5.599)	0.776	10.50	4.0	32.0
Year 2	26	12.54 (6.872)	1.348	11.00	5.0	35.0
Year 3	21	12.67 (6.288)	1.372	12.00	4.0	25.0
Year 4	17	14.35 (9.701)	2.353	12.00	5.0	38.0
Year 5	16	16.13 (10.269)	2.567	12.50	5.0	41.0
Year 6	12	12.92 (4.776)	1.379	12.00	6.0	22.0
Year 7	3	14.67 (7.024)	4.055	14.00	8.0	22.0
Year 8	2	14.50 (6.364)	4.500	14.50	10.0	19.0
BUN (mg/dL) - Change from Baseline [1]						
Month 4	46	-0.82 (4.514)	0.666	0.00	-18.0	6.0
Month 8	54	-0.30 (4.769)	0.649	-1.00	-12.0	14.0
Year 1	52	-0.15 (3.664)	0.508	0.00	-8.0	11.0
Year 2	26	-0.27 (4.788)	0.939	0.00	-12.0	8.0
Year 3	21	-0.71 (5.081)	1.109	0.00	-15.0	11.0
Year 4	17	0.29 (4.089)	0.992	1.00	-6.0	9.0
Year 5	16	1.88 (3.845)	0.961	2.50	-4.0	9.0
Year 6	12	1.42 (3.204)	0.925	1.50	-2.0	8.0
Year 7	3	2.00 (3.606)	2.082	1.00	-1.0	6.0
Year 8	2	2.00 (1.414)	1.000	2.00	1.0	3.0

[1] In general, baseline measurement is defined as the last available value before the subject received the first injection of metreleptin.

Source: Clinical safety Update, Supporting Data Summary 3.3.1.3

Table 58. Creatinine Values and Change from Baseline by Visit

Parameter/Visit	n	Mean (SD)	SE	Median	Min	Max
Creatinine (mg/dL)						
Baseline [1]	69	0.61 (0.270)	0.032	0.58	0.2	1.6
Month 4	46	0.63 (0.294)	0.043	0.60	0.2	1.6
Month 8	54	0.62 (0.348)	0.047	0.53	0.2	2.2
Year 1	52	0.62 (0.310)	0.043	0.56	0.2	1.8
Year 2	26	0.74 (0.527)	0.103	0.60	0.3	2.9
Year 3	21	0.70 (0.336)	0.073	0.60	0.3	1.9
Year 4	17	0.77 (0.420)	0.102	0.60	0.4	2.2
Year 5	16	0.80 (0.502)	0.125	0.76	0.4	2.5
Year 6	12	0.65 (0.232)	0.067	0.65	0.4	1.0
Year 7	4	0.80 (0.249)	0.124	0.76	0.6	1.1
Year 8	2	0.61 (0.028)	0.020	0.61	0.6	0.6
Creatinine (mg/dL) - Change from Baseline [1]						
Month 4	44	0.03 (0.141)	0.021	0.00	-0.3	0.6
Month 8	52	0.04 (0.201)	0.028	0.00	-0.2	1.2
Year 1	51	0.01 (0.136)	0.019	0.00	-0.2	0.4
Year 2	26	0.10 (0.321)	0.063	0.06	-0.2	1.5
Year 3	21	0.10 (0.167)	0.037	0.13	-0.2	0.3
Year 4	17	0.14 (0.178)	0.043	0.20	-0.2	0.6
Year 5	16	0.18 (0.250)	0.062	0.17	-0.2	0.9
Year 6	12	0.12 (0.172)	0.050	0.13	-0.2	0.3
Year 7	4	0.25 (0.127)	0.063	0.24	0.1	0.4
Year 8	2	0.21 (0.028)	0.020	0.21	0.2	0.2

[1] In general, baseline measurement is defined as the last available value before the subject received the first injection of metreleptin.

Source: Clinical Safety Update, Supporting Data Summary 3.3.1.3

Obesity and Investigator-Initiated Trials

In the five integrated obesity trials in the Amgen ISS, there were no adverse events suggestive of nephropathy or renal insufficiency. In metreleptin-treated patients, mean changes from baseline to the last post-baseline assessment were 0.0 mg/dL (as compared to -0.01 mg/dL for placebo) for serum creatinine.

The following renal-related adverse events were reported by the sponsor for the Amgen trials not included in the ISS as well as the metreleptin + pramlintide for obesity clinical program (no further details were provided):

Of the renal adverse events, there were 17 reports of creatine phosphokinase elevated in metreleptin-treated subjects and six in placebo-treated subjects. In addition, there was a single report of azotemia and one report each of hypercalcemia and hypocalcemia in metreleptin-treated patients. The remaining events appeared to be related to either urinary tract infections or frequent urination. All of these events were distributed across the various studies and appeared in a similar incidence in metreleptin and placebo-treated subjects.

Finally, a serious case of diabetic nephropathy and tubulointerstitial nephritis was reported in a patient with CGL who had been receiving metreleptin in an investigator-initiated trial for approximately 10 years; see below.

Table 59. Individual Patient Data for Patients with Renal-related Serious Adverse Events: Metreleptin in Compassionate-Use and Investigator-Initiated Trials

INVESTIGATOR-INITIATED TRIALS				
Indication: LD				
Study ID / Demographics	**Relevant Medical History**	**SAEs**	**Time to Onset**	**Relevant comments**
20020701 30 yr, M, CGL	CGL, diabetes, neurogenic bladder, hepatic steatosis, UTI, diabetic nephropathy, mood disorder	**Diabetic nephropathy** **Tubulointerstitial nephritis** **Hyperkalaemia**	Approximately 10 years	Kidney biopsy showed advanced diabetic nephropathy with chronic interstitial nephritis. Recurrent hyperkalemia secondary to acute renal injury.

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-9

Cardiovascular-Related Adverse Events

Patients with lipodystrophy have elevated TG concentrations, hyperinsulinemia (often with diabetes mellitus), and low levels of HDL-C, which are associated with an increased risk for cardiovascular disease;[31] in particular, patients with Dunnigan-type FPL (*LMNA* mutations).[32] In addition, some patients with lipodystrophy may present with cardiomyopathy or rhythm defects.[31]

The role of leptin on the cardiovascular system has been reviewed (see reference 33); the authors note that elevated serum leptin has been associated with cardiovascular disease including stroke, chronic heart failure, acute myocardial infarction, coronary heart disease, and left cardiac hypertrophy. Nevertheless, observational data can be confounded by the multitude of risk factors that occur in patients with obesity and elevated leptin concentrations.

Experiments in several different rodent models have shown that leptin regulates blood pressure via sympathetic activation, and that hyperleptinemia in obesity can result in hypertension. Further, the mechanisms through which leptin regulates blood pressure, via stimulation of renal sympathetic nerve activity, appear to be intact in the presence of resistance to the weight reducing effects of leptin, supporting the concept of selective central leptin resistance in obesity.[33] Under physiological conditions leptin induces endothelium-dependent vasorelaxation by stimulating nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF). However, at supratherapeutic concentrations, there is evidence that the endothelium becomes resistant to the vasodilating effects of leptin.[34]

Reviewer comment: It is unclear what the impact of replacement or pharmacological doses of metreleptin would be on the endothelium in a leptin-deficient state (and the impact of leptin-deficiency on the vasculature in lipodystrophy).

Patients Treated for Lipodystrophy

In the NIH trials, two (2.8%) patients had a medical history of coronary artery disease, and four (5.6%) patients had cardiomyopathy (n = 2 with hypertrophic cardiomyopathy, n = 1 with cardiomyopathy, and n = 1 with decreased ejection fraction). In the FHA101 trial, seven (28%) of 25 patients with medical history captured had cardiovascular disease (n = 4 with coronary artery disease, n = 1 with aortic atherosclerosis, n = 1 with myocardial infarction, n = 1 with ischemic cardiomyopathy).

Reviewer comment: The discrepancy in cardiovascular disease is likely due to the high proportion of adults (with FPL) in the FHA101 trial. By contrast, over half of the patients in the NIH trials were less than 18 years of age.

In the NIH trials, adverse events in the *Cardiac Disorders* SOC were reported in three (4.2%) of 72 lipodystrophy patients and are summarized in the table below, along with other adverse events relevant to the cardiovascular system but coded under other SOCs (i.e., *General*, *Vascular*, *Investigations*). One adverse event in the *Cardiac Disorders* SOC had a fatal outcome (Patient 90125, cardiac arrest) in the setting of pancreatitis and septic shock (see Section 7.3.1, Deaths). The serious adverse event of worsening hypertension (Patient 90105) was assessed as related; see Section 7.3.2, Nonfatal Serious Adverse Events. In addition, a non-serious adverse event of chest pain (Patient 90106) was assessed as related. No further information on this adverse event of chest pain in Patient 90106 is available. There were no cases of congestive heart failure reported in the NIH trials.

In FHA101, no adverse events in the *Cardiac Disorders* SOC were reported, but two events of chest pain (*General Disorders* SOC) and two events of increased blood pressure (*Investigations* SOC), one of which occurred in a patient with an adverse event of chest pain, were reported. There were no cases of congestive heart failure reported in FHA101.

Table 60. Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to the Cardiovascular System, NIH and FHA101 Trials

Patient ID / Demog	Relevant Medical History	TEAE[1] (SOC)	Time to Onset (Days)	Investigator Assessment of Relatedness / SAE
NIH Studies 991265/20010769				
90101 17 yr F, AGL	Pancreatitis, diabetes mellitus, hypertriglyceridemia, steatohepatitis, anxiety	Palpitations Tricuspid valve incompetence (both Cardiac)	2006 349	Unrelated – non SAE Unrelated – non SAE
90105 14 yr F, CGL	Tachycardia, hypertension, diabetes, steatohepatitis, proteinuria Baseline BP 149/85, HR 105	Worsening of hypertension (Vascular) Tachycardia associated with worsening of hypertension (Cardiac)	0[2] 0[2]	Related – SAE Related – Non SAE
90106 35 yr F, CGL	Endocarditis, peripheral vascular disease, amputated left great toe, diabetes, hyperlipidemia, deep vein thrombosis, smoking, avascular necrosis, left shoulder pain	Chest pain (General)	11	Related – Non SAE
90107 42 yr F, FPL	Coronary artery disease, multiple stent placements, stable angina, hypertension, hypertriglyceridemia, diabetes mellitus, focal glomerulo-nephritis, stage IV kidney failure, proteinuria, recurrent pancreatitis	Cardiac catherization (Investigations)	2657	Unrelated SAE
90110 8 yr F, AGL	Asthma, Kawasaki's disease, hypertriglyceridemia, diabetes, mild proteinuria	Chest tightness (General)	194	Unrelated SAE
90111 13 yr M, CGL	Diabetes, proteinuria, diabetic retinopathy	Persistent recurrent chest pain (General)	242	Unrelated – Non SAE
90125 15 yr F, CGL	Hypertension, diabetes, pancreatitis, hyperlipidemia, baseline TG 1669 mg/dL, focal segmental glomerulosclerosis	Cardiac arrest (Cardiac)	106	Unrelated fatal SAE
90163 20 yr F, CGL	Hypertriglyceridemia, insulin resistance, polycystic ovary disease, fatty liver, proteinuria	Hypertension (Vascular)	135	Unrelated – Non SAE
Study FHA101				
648003 58 yr F, FPL	Coronary artery disease, hypertension, CABG, GERD, fatty liver, back and neck pain, lipid abnormalities, diabetes, hyperthyroidism	Chest pains (General)	500	Unrelated SAE
648013 23 yr F, FPL	Hypertension, increased cholesterol, increased triglycerides, diabetes, fatty liver, hyperandrogenism	Blood pressure elevation (Investigations)	364[3]	Unrelated – Non SAE
648019 55 yr F, FPL	High cholesterol, hypertension, ablation for supraventricular tachycardia (aberrant pathway), high cholesterol, high triglycerides, asthma, fatty liver, myopathy	Increased blood pressure (Investigations) Chest pain (General)	112 136	Related– Non SAE Unrelated – Non SAE

Yr = years; F = female; M = male; TG = triglycerides; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy; LFT = liver function tests; TEAE = treatment-emergent adverse event; SOC = system organ class.

[1] Verbatim.
[2] Event occurred after first injection of metreleptin treatment.
[3] Start day unknown, calculation based on the 1st of the month and year.

Source: Clinical Safety Update, Table 44

The following table summarizes the change in systolic and diastolic blood pressure in those patients with available data up to one year of metreleptin treatment as well as for patients with elevated baseline values (SBP 130 mmHg or greater, DBP 90 mmHg or greater).

Table 61. Mean Change from Baseline in Systolic and Diastolic Blood Pressure by Visit, NIH Trials

SBP	All Patients			Baseline SBP ≥130 mmHg		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	62	128.0	NA	26	143.0	NA
Month 4	35	130.1	-5.6	14.	146.9	-9.6
Month 8	41	129.8	-7.5	18	144.3	-15.3
Month 12	33	127.7	-7.1	12	141.8	-17.3
DBP	**All Patients**			**Baseline DBP ≥90 mmHg**		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	62	71.3	NA	6	92.3	NA
Month 4	35	71.9	-2.5	4	92.5	-12.0
Month 8	41	71.8	-1.6	3	92.3	-17.3
Month 12	33	70.4	+1.0	2	93.5	-13.5

BL = baseline; SBP = systolic blood pressure; DBP = diastolic blood pressure.
In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin.
Baseline blood pressure values are shown only for those patients who had blood pressure data at a certain time point.

Source: Clinical Safety Update, Table 29

Reviewer comment: As noted previously (reviewer comment) regarding evaluating a subset of patients with higher baseline values for the efficacy parameters, the observation of greater decreases from baseline might be expected in this select population (i.e., regression to the mean). The increased decreases from baseline observed in the subgroups with elevated SBP and DBP should therefore be interpreted with caution.

For those NIH patients with available baseline heart rate data (63 of 72), the mean (± SD) baseline heart rate was 92 (± 15.3) bpm. Mean (± SE) decreases from baseline in heart rate during the first year of treatment were -6.9 (± 2.2) bpm at Month 8 (n = 43) and -2.4 (± 3.1) bpm at Year 1 (n = 33).

The following table lists the patients having increases in systolic and diastolic blood pressure 10 mmHg or greater or 15 mmHg or greater at two or more consecutive visits. Two patients (90129, 90130) meeting the criteria for increases in both systolic blood pressure and diastolic blood pressure by greater than or equal to 10 and 15 mmHg for two or more consecutive times also met criteria for systolic BP 20 mmHg or greater for

two or more consecutive times. No patients had increase in diastolic blood pressure 20 mmHg or greater at two or more consecutive visits.

Table 62. Categorical Summary of Increases in Vital Sign Measurements, NIH Trials

Vital Sign Category	Generalized Lipodystrophy n (%) [RPY]	Partial Lipodystrophy n (%) [RPY]	All Patients n (%) [RPY]
Heart Rate (beats/min)			
N with a BL and at least 1 post-BL measurement	**39**	**20**	**59**
Increased by ≥5 bpm from BL at least 1 time	21 (53.8) [0.226]	9 (45.0) [0.145]	30 (50.8) [0.194]
Increased by ≥10 bpm from BL at least 1 time	12 (30.8) [0.107]	8 (40.0) [0.122]	20 (33.9) [0.112]
Increased by ≥15 bpm from BL at least 1 time	8 (20.5) [0.062]	5 (25.0) [0.071]	13 (22.0) [0.065]
Increased by ≥20 bpm from BL at least 1 time	3 (7.7) [0.019]	3 (15.0) [0.037]	6 (10.2) [0.025]
N with a BL and at least 2 post-BL measurements	**34**	**19**	**53**
Increased by ≥5 bpm from BL at 2 or more consecutive visits	6 (17.6) [0.043]	6 (31.6) [0.087]	12 (22.6) [0.057]
Increased by ≥10 bpm from BL at 2 or more consecutive visits	3 (8.8) [0.019]	2 (10.5) [0.024]	5 (9.4) [0.021]
Increased by ≥15 bpm from BL at 2 or more consecutive visits	1 (2.9) [0.006]	2 (10.5) [0.024]	3 (5.7) [0.012]
Increased by ≥20 bpm from BL at at least 2 consecutive visits	1 (2.9) [0.006]	2 (10.5) [0.024]	3 (5.7) [0.012]
Systolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**39**	**20**	**59**
Increased by ≥5 mmHg from BL at least 1 time	20 (51.3) [0.213]	11 (55.0) [0.198]	31 (52.5) [0.207]
Increased by ≥10 mmHg from BL at least 1 time	15 (38.5) [0.111]	8 (40.0) [0.123]	23 (39.0) [0.115]
Increased by ≥15 mmHg from BL at least 1 time	9 (23.1) [0.059]	8 (40.0) [0.121]	17 (28.8) [0.078]
Increased by ≥20 mmHg from BL at least 1 time	8 (20.5) [0.051]	3 (15.0) [0.040]	11 (18.6) [0.048]
N with a BL and at least 2 post-BL measurements	**34**	**19**	**53**
Increased by ≥5 mmHg from BL at 2 or more consecutive visits	6 (17.6) [0.042]	7 (36.8) [0.111]	13 (24.5) [0.063]
Increased by ≥10 mmHg from BL at 2 or more consecutive visits	4 (11.8) [0.026]	4 (21.1) [0.052]	8 (15.1) [0.035]
Increased by ≥15 mmHg from BL at 2 or more consecutive visits	2 (5.9) [0.013]	3 (15.8) [0.037]	5 (9.4) [0.021]
Increased by ≥20 mmHg from BL at 2 or more consecutive visits	1 (2.9) [0.006]	1 (5.3) [0.012]	2 (3.8) [0.008]
Diastolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**39**	**20**	**59**
Increased by ≥5 mmHg from BL at least 1 time	24 (61.5) [0.270]	15 (75.0) [0.434]	39 (66.1) [0.316]
Increased by ≥10 mmHg from BL at least 1 time	14 (35.9) [0.110]	11 (55.0) [0.205]	25 (42.4) [0.138]
Increased by ≥15 mmHg from BL at least 1 time	7 (17.9) [0.047]	5 (25.0) [0.067]	12 (20.3) [0.054]
Increased by ≥20 mmHg from BL at least 1 time	5 (12.8) [0.031]	3 (15.0) [0.037]	8 (13.6) [0.033]
N with a BL and at least 2 post-BL measurements	**34**	**19**	**53**
Increased by ≥5 mmHg from BL at 2 or more consecutive visits	10 (29.4) [0.076]	7 (36.8) [0.110]	17 (32.1) [0.087]
Increased by ≥10 mmHg from BL at 2 or more consecutive visits	4 (11.8) [0.027]	4 (21.1) [0.056]	8 (15.1) [0.037]
Increased by ≥15 mmHg from BL at 2 or more consecutive visits	2 (5.9) [0.013]	2 (10.5) [0.025]	4 (7.5) [0.017]
Increased by ≥20 mmHg from BL at 2 or more consecutive visits	0 (0.0) [0.000]	0 (0.0) [0.000]	0 (0.0) [0.000]

BL = baseline.

Notes: [RPY] = Rate per Patient Year, derived by dividing n by patient years of exposure. If a patient had the event, their exposure is truncated at the time of first event.

- Baseline measurement is defined as the last available value before the patient received the first injection of metreleptin.

Source: Clinical Safety Update, Table 30

Table 63. Individual Patient Listing of Blood Pressure Increases at Two or More Consecutive Visits, NIH Trials

Patient ID / Demog	Relevant Medical History	Baseline BP (mmHg)	Systolic BP increase From Baseline for ≥2 Consecutive Visits (mmHg)		Diastolic BP Increase From Baseline for ≥2 Consecutive Visits (mmHg)		Summary of Post-Treatment Measurements and Relevant AEs
			≥10 (n = 8)	≥15 (n = 5)	≥10 (n = 8)	≥15 (n = 4)	
90109 13 yr F, AGL	Diabetes, proteinuria	122/63 to 133/86 (M8)	X				BP increased to 136/72 mmHg at Month 2 (max), 132/70 mmHg at Month 4, and 133/86 mmHg at Month 8 (last available measurement).
90110 8 yr F, AGL	Diabetes, mild proteinuria, Kawasaki's disease	108/70 to 125/64 (Y 6.5)	X				BP generally in normal range except 139/77 mmHg at Year 5 (max). BP 121/69 mmHg at Year 6, and 125/64 mmHg at last visit at Month 78.
90113 12 yr F, CGL	Diabetes Proteinuria (on Ramipril)	129/63 to 134/74 (Y6)			X		BP generally in borderline range. At Month 12 and 18, BP was 127/74 mmHg and 126/74 mmHg. BP was 137/79 mmHg at Month 30 (max DBP), 142/72 at Month 36 (max SBP) 130/74 mmHg at Month 42, and 134/74 mmHg at Year 6. Developed focal segmental glomerulosclerosis around Y1.
90117 45 yr F, FPL	Hypertension (on metoprolol)	116/62 to 122/67 (Y8)			X		BP generally in normal to borderline range. At Month 30 and 36, BP was 120/78 mmHg (max DBP) and 136/72 mmHg (max SBP). BP 122/65 mmHg at Year 6.
90120 23 yr F, CGL	Diabetes Anxiety Proteinuria	121/55 to 118/68 (Y8)			X	X	BP generally in normal range, and all DBP values within normal range. Maximum DBP 75 mmHg at Y2. At Month 60 and 71, BP was 126/71 mm Hg and 129/73 mmHg. At Year 6, BP 129/73 (max SBP).
90123 43 yr F, FPL	Hypertension Diabetes	98/58 to 113/58 (Y7)	X	X			All BP in normal range. At Y6 and Y7, BP was 115/60 (max SBP) and 113/58 mmHg.
90128 15 yr M, AGL	Diabetes Intermittent dehydration	96/58 to 134/84 (Y6)	X	X			BP generally normal for 4 years except125/73 at Y3. At Y4, BP 109/65. Then next BP (last available) at Y6 was 134/84 mmHg (max).
90129* 34 yr F, FPL	Hypertension Diabetic nephropathy	125/73 to 154/92 (Y2)	X	X	X	X	BP increased several months of treatment and remained elevated - 139/85 at M4, 152/79 at M8, 144/94 at M12 (max DBP), 160/92 at M12 (max SBP), 154/92 at Y2 (last available). No relevant TEAEs noted.
90130* 7 yr F, CGL	Hypertrophic cardiomyopathy Diabetes	117/59 to 118/69 (Y6)	X	X	X	X	BP normal first year. At Month 18, 24 and 30, BP was 129/74 mmHg, 140/80 mmHg and 140/71 mmHg. Subsequent to that, BP was generally in the normal range. No TEAEs reported.
90138 34 yr F, FPL	Diabetes Anxiety	127/67 to 114/67 (Y4.5)			X	X	BP generally in normal to borderline range. At Month 4 and 12, BP was 124/87 mmHg (max DBP) and 126/83 mmHg.
90141 10 yr F, APL	Diabetes	110/78 to 111/74 (Y3.5)	X				BP generally in normal to borderline range. At Month 8 and 12, BP was 126/71 mmHg (max SBP) and 123/77 mmHg. All other BP measurements normal.
90152 30 yr F, FPL	Preeclampsia Diabetes	134/77 to 141/88 (M18)			X		Only 2 post-treatment measures. At M8, BP was 134/89 mmHg, and at Month 18, BP was 141/88 mmHg.
90163 20 yr F, CGL	Nephromegaly Proteinuria Diabetes	144/75 to 144/89 (M18)			X		Hypertensive at baseline and BP remained in similar range. At Month 8 and 18, BP was 142/86 mmHg and 144/89 mmHg (max DBP). At M4, patient had a non SAE of hypertension (started on lisinopril) and also diagnosed with focal segmental glomerulosclerosis at same time.
90166 2 yr F, FPL	No relevant medical history	87/43 to 102/62 (Y1)	X	X			Only 2 post-treatment measures. At Month 8 and 12, BP was 105/48 and 102/62 mmHg.

Yr = years; BP = blood pressure; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.
*Also met criteria for SBP increase ≥20 mmHg at 2 or more consecutive visits

Source: Clinical Safety Update, Table 31

The following table lists the five patients having increases in heart rate 10 bpm or greater or 15 bpm or greater at two or more consecutive visits. The baseline and last available heart rate measurements for these patients were all in the normal range (less than 100 bpm).

Table 64. Individual Patient Listing of Heart Rate Increases at Two or More Consecutive Visits, NIH Trials

Patient ID / Demog	Relevant Medical History	Baseline to Last Available (BPM)	Heart Rate Increase From Baseline for ≥2 Consecutive Visits (BPM)		Summary of Post-Treatment Measurements and Relevant AEs
			≥10 (n = 8)	≥15 (n = 5)	
90109 13 yr F, AGL	Diabetes proteinuria	95 to 98 (M8)	X		HR 101 (M1), 108 (M2), 125 (M4)
90124 17 yr M, CGL	Diabetes	75 to 82 (Y6)	X		HR generally in 70-90 range. Maximum heart rate 91 (Y1)
90130 7 yr F, CGL	Hypertrophic cardiomyopathy Diabetes	86 to 89 (Y6)	X	X	HR 129 at M4 (max) and remained elevated 101-115 first 2 yrs. From Y3 to Y6, HR in 80-90s except 101 (Y5).
90144 10 yr F, APL	Hypertension	55 to 98 (Y3.5)	X	X	HR 103 at M8 (first measurement), all subsequent values >100, max 132 at M18, except 2 measurements of 98.
90157 30 yr F, FPL	Hypertension Pre-eclampsia Palpitations Diabetes	56 to 86 (Y2)	X	X	Only 2 post-treatment measures. 85 at Y1, 86 at Y2.

Yr = years; HR = heart rate; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.
Source: Clinical Safety Update, Table 32

The following table summarizes the change in systolic and diastolic blood pressure in those patients with available data up to two years of metreleptin treatment as well as for patients with elevated baseline values (SBP 130 mmHg or greater) in FHA101. There were no patients with baseline DBP 90 mmHg or greater.

Table 65. Mean Change from Baseline in Systolic and Diastolic Blood Pressure by Visit, FHA101

SBP	All Patients			Baseline SBP ≥130 mmHg		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	25	133.3	NA	15	142.4	NA
Month 1	24	133.3	-6.6	14	143.1	-7.9
Month 12	10	133.9	-6.6	7	142.6	-8.9
Month 24	6	130.5	-14.5	4	139.3	-21.5
DBP	**All Patients**			**Baseline DBP ≥90 mmHg**		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	25	74.1	NA	0	NA	NA
Month 1	24	73.8	-3.2	0	NA	NA
Month 12	10	73.4	-3.1	0	NA	NA
Month 24	6	69.0	-3.3	0	NA	NA

BL = baseline; SBP = systolic blood pressure; DBP = diastolic blood pressure; NA = not applicable.
In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin.
Baseline blood pressure values are shown only for those patients who had blood pressure data at a certain time point.

Source: Clinical Safety Update, Table 38

For those FHA101 patients with available baseline heart rate data (25 of 28), the mean (± SD) baseline heart rate was 79.2 (± 13.7) bpm. A small mean (± SE) decrease in heart rate was seen at Month 1 (-1.0 ± 2.0 bpm, n = 24); thereafter, the decrease was generally in the range of -4.0 bpm to -6.0 bpm to Month 33.

The following table presents categorical analyses of heart rate, systolic and diastolic blood pressure by increases of greater than or equal to 5, 10, 15, and 20 beats per minute (heart rate) or mmHg (systolic and diastolic blood pressure) at least one time or at two or more consecutive visits.

Table 66. Categorical Summary of Vital Signs Increases, FHA101

Vital Sign Category	Generalized Lipodystrophy (N = 5) n (%) [RPY]	Partial Lipodystrophy (N = 23) n (%) [RPY]	All Patients (N = 28) n (%) [RPY]
Heart Rate (beats/min)			
N with a BL and at least 1 post-BL measurement	**3**	**22**	**25**
Increased ≥5 bpm from BL at least 1 time	1 (33.3) [0.51]	13 (59.1) [0.96]	14 (56.0) [0.90]
Increased ≥10 bpm from BL at least 1 time	0 (0.0) [0.00]	10 (45.5) [0.59]	10 (40.0) [0.46]
Increased ≥15 bpm from BL at least 1 time	0 (0.0) [0.00]	5 (22.7) [0.21]	5 (20.0) [0.17]
Increased ≥20 bpm from BL at least 1 time	0 (0.0) [0.00]	2 (9.1) [0.08]	2 (8.0) [0.07]
N with a BL and at least 2 post-BL measurements	**3**	**19**	**22**
Increased ≥5 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	8 (42.1) [0.43]	8 (36.4) [0.34]
Increased ≥10 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	3 (15.8) [0.12]	3 (13.6) [0.10]
Increased ≥15 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Increased ≥20 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Systolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**3**	**22**	**25**
Increased ≥5 mm Hg from BL at least 1 time	1 (33.3) [0.51]	11 (50.0) [0.71]	12 (48.0) [0.68]
Increased ≥10 mm Hg from BL at least 1 time	1 (33.3) [0.51]	7 (31.8) [0.37]	8 (32.0) [0.38]
Increased ≥15 mm Hg from BL at least 1 time	1 (33.3) [0.22]	5 (22.7) [0.24]	6 (24.0) [0.24]
Increased ≥20 mm Hg from BL at least 1 time	0 (0.0) [0.00]	3 (13.6) [0.13]	3 (12.0) [0.11]
N with a BL and at least 2 post-BL measurements	**3**	**19**	**22**
Increased ≥5 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	5 (26.3) [0.24]	6 (27.3) [0.27]
Increased ≥10 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	4 (21.1) [0.17]	5 (22.7) [0.20]
Increased ≥15 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	2 (10.5) [0.08]	2 (9.1) [0.07]
Increased ≥20 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Diastolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**3**	**22**	**25**
Increased ≥5 mm Hg from BL at least 1 time	1 (33.3) [0.51]	13 (59.1) [0.98]	14 (56.0) [0.92]
Increased ≥10 mm Hg from BL at least 1 time	1 (33.3) [0.51]	5 (22.7) [0.23]	6 (24.0) [0.25]
Increased ≥15 mm Hg from BL at least 1 time	1 (33.3) [0.36]	0 (0.0) [0.00]	1 (4.0) [0.03]
Increased ≥20 mm Hg from BL at least 1 time	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
N with a BL and at least 2 post-BL measurements	**3**	**19**	**22**
Increased ≥5 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	3 (15.8) [0.13]	4 (18.2) [0.16]
Increased ≥10 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	0 (0.0) [0.00]	1 (4.5) [0.03]
Increased ≥15 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Increased ≥20 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]

BL = Baseline.
Notes: [RPY] = Rate per Patient Year, derived by dividing n by patient years of exposure. If a patient had the event, their exposure is truncated at the time of first event.
-Baseline measurement is defined as the last available value before the patient received the first injection of metreleptin.
Source: Clinical Safety Update, Table 39

The following table presents an individual patient listing of increases in systolic and diastolic blood pressure (greater than or equal to 10 or 15 mmHg) at two or more consecutive visits.

Table 67. Individual Patient Listing of Blood Pressure Increases at Two or More Consecutive Visits, FHA101

Patient Number / Demog	Relevant Medical History	Baseline to Last Available (mmHg)	Systolic BP Increase From Baseline for ≥2 Consecutive Visits (mmHg)		Diastolic BP Increase From Baseline for ≥2 Consecutive Visits (mmHg)		Summary of Post-Treatment Measurements and Relevant AEs
			≥10 (n = 5)	≥15 (n = 2)	≥10 (n = 1)	≥15 (n = 0)	
648001 9 yr F, AGL	Increased QT interval, atenolol for increased heart rate, lisinopril for proteinuria	110/51 to 112/65 (M35)	X		X		SBP 90's-120's (max 126 at M33). DBP 50's-60's (max 67 at M28).
648009 57 yr F, FPL	Hypertension (on HCTZ, amlodipine and enalapril), diabetes, anxiety	135/67 to 130/73 (Y2)	X	X			At M6 and M 9, BP was 168/66 and 150/70 mmHg, and returned back to baseline at M21 and M24 (129/59 and 130/73). SBP 130's-160's (max 168 at M6). DBP 60's-70's.
648011 62 yr F, FPL	Hypertension (on amlodipine, lisinopril, metoprolol), CAD, diabetes, anxiety	134/74 to 132/72 (M18)	X	X			SBP 130's-150's (max 154 at M12). DBP 60's-80's.
648017 58 yr M, FPL	Ischemic cardiomyopathy (on lisinopril), 3 stents, ICD implanted, Diabetes	132/60 to 138/63 (M9)	X				SBP 130's-150's (max 149 at M3). DBP 60's (max 65 at M3).
648019 55 yr F, FPL	Hypertension (on lisinopril, spironolactone)	133/82 to 107/74 (M9)	X				At M2, BP was 143/88. Non SAE of 'blood pressure increased' at M3 (BP 146/94). BP subsequently decreased to below baseline.

Yr = years; BP = blood pressure; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.
Source: Clinical Safety Update, Table 40

No patient had increases in heart rate by greater than or equal to 15 or 20 bpm at two or more consecutive visits. Three patients (648011, 648019, 648021) had increases in heart rate of 10 bpm or greater at two or more consecutive visits. All three patients had a history of hypertension and were receiving anti-hypertensive treatment. The maximum heart rate for all three patients was less than 100 bpm.

Patients Treated for Obesity

In the five integrated obesity trials in the Amgen ISS, adverse events in the *Cardiac Disorders* SOC had a higher overall incidence in obese patients treated with metreleptin (n = 14, 1.8%) than obese patients treated with placebo (n = 1, 0.3%). Cardiac adverse

events in metreleptin-treated patients were distributed across the following preferred terms: angina (n = 4), aortic valve disease (n = 1), arrhythmia (n = 1), atrial fibrillation (n = 1), extrasystoles (n = 1), palpitations (n = 4), sinus tachycardia (n = 1), tachycardia (n = 3), and ventricular arrhythmia (n = 1). One placebo-treated patient had a cardiac adverse event of palpitations. Four patients (all metreleptin-treated) experienced a serious adverse event in the *Cardiac Disorders* SOC [preferred terms: angina pectoris (n = 2), atrial fibrillation, ventricular arrhythmia]. In addition, under the *Investigations* SOC, three serious adverse events were reported: irregular heart rate (one metreleptin-treated, one placebo-treated) and increased blood pressure (placebo-treated).

Reviewer comment: The imbalance in cardiac events between metreleptin and placebo is noted, however the individual preferred terms are from a variety of cardiac conditions, and do not necessarily point to any a single underlying cardiac diagnosis. The narrative for the serious adverse event of ventricular arrhythmia is presented in Section 7.3.2, Nonfatal Serious Adverse Events.

The incidence of categorical increases of heart rate, systolic and diastolic blood pressure were higher in the metreleptin treatment groups than in the placebo treatment group, however the differences were small.

Table 68. Patients Meeting Criteria for Categorical Vital Sign Analyses, Amgen Obesity ISS, N = 1072

		Placebo		All Metreleptin	
Vital Sign	Criteria	Patients Meeting Criteria at Least 1 Time N (%) [RPY]	Patients Meeting Criteria ≥2 Consecutive Times N (%) [RPY]	Patients Meeting Criteria at Least 1 Time N (%) [RPY]	Patients Meeting Criteria ≥2 Consecutive Times N (%) [RPY]
Heart Rate (beat/min)	Increase ≥10	148 (43.3) [1.91]	51 (15.5) [0.51]	352 (45.2) [2.35]	123 (16.3) [0.65]
	Increase ≥15	76 (22.2) [0.80]	18 (5.5) [0.17]	191 (24.6) [1.05]	44 (5.8) [0.21]
	Increase ≥20	40 (11.7) [0.39]	5 (1.5) [0.05]	87 (11.2) [0.43]	15 (2.0) [0.07]
Systolic BP (mm Hg)	Increase ≥10	165 (48.2) [2.21]	72 (22.0) [0.77]	386 (49.6) [2.79]	180 (23.8) [1.01]
	Increase ≥15	104 (30.4) [1.14]	25 (7.6) [0.24]	253 (32.5) [1.50]	87 (11.5) [0.44]
	Increase ≥20	59 (17.3) [0.59]	11 (3.4) [0.10]	142 (18.3) [0.74]	39 (5.2) [0.19]
Diastolic BP (mm Hg)	Increase ≥10	120 (35.1) [1.40]	48 (14.6) [0.48]	300 (38.6) [1.86]	115 (15.2) [0.60]
	Increase ≥15	55 (16.1) [0.55]	14 (4.3) [0.13]	128 (16.5) [0.66]	44 (5.8) [0.21]
	Increase ≥20	21 (6.1) [0.20]	4 (1.2) [0.04]	59 (7.6) [0.28]	18 (2.4) [0.08]

Source: Clinical Safety Update, Table 54

In metreleptin-treated patients, the mean changes from baseline to the last post-baseline assessment were -1.6 mmHg (versus -1.1 for placebo) for systolic blood

pressure, -1.1 mm Hg (versus -0.7 for placebo) for diastolic blood pressure, and -0.4 bpm (versus -1.2 for placebo) for heart rate.

In the Amgen and Amylin obesity trials not included in the ISS, the following adverse events related to the cardiovascular system were tabulated by the sponsor. No denominators were provided in this table; however, it appears 1228 patients were exposed to metreleptin and approximately 400 patients to placebo in the non-ISS obesity trials combined. Given that these trials varied significantly in terms of study duration and inclusion of a placebo arm, the sponsor has not attempted to conduct analyses of integrated data across trials.

The adverse event of 'cardiac arrest' was described in Section 7.3.2, Nonfatal Serious Adverse Events.

Table 69. Cardiovascular Adverse Events, Additional Obesity Trials (non-ISS)

Cardiovascular Adverse Events	Metreleptin	Placebo
Preferred Term		
Aneurysm	1	0
Cardiac arrest	1	0
Coronary artery disease	1	0
Cardiac enzyme elevated	1	0
Cardiac murmurs (type not specified)	4	2
Hypertension	8	3
Miscellaneous rhythm abnormalities (tachycardia, bradycardia, palpitations, etc.)	16	5
Peripheral ischemia	1	0

Source: Response to FDA Clinical Q1 (24 May 2013), Table 1.4.5

Psychiatric Adverse Events

Because metreleptin is a centrally-acting product that affects appetite, it is possible that it might impact other central sites that affect reward, mood, and behavior. Evaluations of neuropsychiatric function, including suicidality assessments, are recommended in the development of products to treat obesity.[35] Utilizing the 2013 data cutoff, 11% of patients in the NIH trials and 9% of patients in the FHA101 trial experienced a psychiatric adverse event. One adverse event each of panic reaction, paranoia, and suicidal ideation********** in the NIH trials and one adverse event of suicidal ideation in the FHA101 trials were considered serious. Narratives are presented in Section 7.3.2, Serious Adverse Events.

********** Note that the adverse event of "suicidal ideation" was in fact a suicide attempt (see Section 7.3.2, Nonfatal serious adverse events). This adverse event is miscoded.

Table 70. Psychiatric Disorders Adverse Events, NIH Trials (2013 Data Cut)

	N=90 n (%)
Psychiatric Disorders	10 (11.1)
Anxiety	3 (3.3)
Depression	2 (2.2)
Insomnia	2 (2.2)
Bipolar disorder	1 (1.1)
Hallucinations, mixed	1 (1.1)
Panic reaction	1 (1.1)
Paranoia	1 (1.1)
Suicidal ideation	1 (1.1)

Source: Four-Month Safety Update, Protocol 991265 and 20010769 Supporting Data Summary 3.2.1.3

Table 71. Psychiatric Disorders Adverse Events, FHA101 (2013 Data Cut)

	N=35 n (%)
Psychiatric Disorders	3 (8.6)
Anxiety	3 (8.6)
Suicidal ideation	1 (2.9)

Source: Four-Month Safety Update, FHA101 Supporting Data Summary 3.2.1

In the obesity trials, psychiatric adverse events overall were similar in the metreleptin- and placebo-treated groups. Slight imbalances of unknown significance (metreleptin greater than placebo) was seen for adverse events of depression (including depressed mood), and adverse events related to sleep (insomnia, sleep disorder, etc.).

Table 72. Adverse Events from Psychiatric Disorders SOC, ISS Data (Amgen Obesity Trials)

	Metreleptin N=784	**Placebo N=351**
Psychiatric Disorders	49 (6.3)	21 (6.0)
Insomnia	17 (2.2)	7 (2.0)
Depression	12 (1.5)	4 (1.1)
Anxiety	7 (0.9)	5 (1.4)
Depressed mood	7 (0.9)	1 (0.3)
Stress	3 (0.4)	2 (0.6)
Sleep disorder	3 (0.4)	0
Libido decreased	1 (0.1)	1 (0.3)
Nervousness	1 (0.1)	1 (0.3)
Tearfulness	1 (0.1)	1 (0.3)
Abnormal dreams	1 (0.1)	0
Emotional disorder	1 (0.1)	0
Initial insomnia	1 (0.1)	0
Mood swings	1 (0.1)	0
Terminal insomnia	1 (0.1)	0

Source: Reviewer-generated from ISS dataset (iss dae.xpt)

***Post-Review Addendum*: CPK-Related Adverse Events**

A very high creatine phosphokinase (CPK) value was noted during review of the transaminase data (Patient 90163, 11422 U/L on visit 3). CPK was not routinely measured during the lipodystrophy trial; only six patients had any CPK values (mostly single values) reported in the datasets. The sponsor responded to the query about this patient as follows:

Patient 90163 with a very high CPK measurement was a 20-year old female at study entry with medical history of CGL, fatty liver, hepatosplenomegaly, nephromegaly, proteinuria, PCOS, hypertriglyceridemia, insulin resistance, and diabetes. The patient started metreleptin therapy in 04 January 2010. At the Week 8 visit (01 April 2010), the patient's CPK was 11,422 IU/L. BUN and creatinine were normal at 11 and 0.69 mg/dL, respectively, and other chemistry values including potassium, magnesium, and phosphorus were within the normal range. The site noted that the patient was a (b) (6) *track runner who was in training when her blood work was collected. No AEs related to muscle symptoms were reported for this patient. No baseline or additional CPK values were available. The patient continued on metreleptin with follow-up chemistries that remained within the normal range.*

Additional information regarding myopathy and CPK in the lipodystrophy and obesity trials was requested and provided by the sponsor. The sponsor stated that there were no reported events of myopathy or rhabdomyolysis in any metreleptin-treated patient in either the Amylin or Amgen obesity programs, or from the lipodystrophy programs.

One adverse event of CPK elevation was reported in a lipodystrophy patient (Patient 90106) enrolled in the NIH studies. This patient had a relevant medical history of myoclonic jerks and experienced a serious adverse event of exacerbation of weakness in left lower extremity and exacerbation of myoclonic jerks. The patient was a 35-year-old female at study entry with CGL, diabetes, lower extremity weakness, myoclonic jerks, hyperlipidemia, polycystic ovarian syndrome (PCOS), endocarditis, and peripheral vascular disease. The patient was hospitalized due to these events on Day 2 of metreleptin treatment ((b) (6)). Metreleptin was interrupted during the hospitalization. On 13 Sep 2000, the patient was reported to have an adverse event of elevated CPK (793 U/L). On the following day, CPK was within normal range (108 U/L) and the other events resolved. The patient resumed metreleptin therapy on 15 Nov 2000, with no further CPK or muscle-related adverse events.

In the Amylin metreleptin + pramlintide program, the incidence of adverse events of CPK elevation for the metreleptin treatment groups (including both metreleptin monotherapy and metreleptin in combination with pramlintide) was reported to be 2.5% (17/693), compared with 3.3% (4/133) for the pramlintide monotherapy treatment groups, and 5.4% (6/111) for the placebo treatment group.

No event of CPK elevation was reported in the Amgen obesity program.

Reviewer comment: Myopathy has been described in patients with lipodystrophy.[36] Given the limited data, it is unknown whether metreleptin could exacerbate myopathy in patients who are predisposed to it.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Patients Treated for Lipodystrophy

The following table presents the adverse events with incidence of 5% or greater in the 72 patients in order of decreasing incidence in the NIH trial. For comparison, the updated incidence from the four-month safety update (N = 90) is included, as well as the common adverse events from the FHA101 trial (N = 28) and four-month safety update (N = 35).

Reviewer comment: Pronounced differences in incidences of some adverse event preferred terms are noted in the NIH trials as compared with the FHA101 trial (Table 73). Some of the differences may be due the small numbers of patients; however, differences may also be attributed to the differences in the patient populations, the dosing algorithm, or ascertainment of adverse events between the trials / study sites.

Table 73. Frequent (Incidence 5% or Greater) Treatment-Emergent Adverse Events by Preferred Term in Patients Receiving Metreleptin, NIH and FHA101 Trials (with Four-Month Safety Update Data)

	NIH		FHA101	
Preferred Term	**BLA N=72 n (%)**	**4-month safety update N=90 n (%)**	**BLA N=28 n (%)**	**4-month safety update N=35 n (%)**
Hypoglycemia	8 (11.1)	10 (11.1)	7 (25.0)	12 (34.3)
Fatigue	7 (9.7)	7 (7.8)	2 (7.1)	2 (5.7)
Headache	6 (8.3)	7 (7.8)	2 (7.1)	3 (8.6)
Nausea	6 (8.3)	7 (7.8)	10 (35.7)	12 (34.3)
Weight decreased	6 (8.3)	13 (14.4)	2 (7.1)	2 (5.7)
Abdominal pain	5 (6.9)	10 (11.1)	5 (17.9)	5 (14.3)
Alopecia	5 (6.9)	6 (6.7)	0	0
Ovarian cyst	5 (6.9)	6 (6.7)	1 (3.6)	1 (2.9)
Pain in extremity	5 (6.9)	5 (5.6)	0	0
Upper respiratory tract infection	5 (6.9)	6 (6.7)	5 (17.9)	7 (20.0)
Arthralgia	4 (5.6)	7 (7.8)	0	0
Constipation	4 (5.6)	4 (4.4)	1 (3.6)	1 (2.9)
Diarrhea	4 (5.6)	4 (4.4)	0	0
Dizziness	4 (5.6)	4 (4.4)	2 (7.1)	3 (8.6)
Ear infection	4 (5.6)	5 (5.6)	1 (3.6)	3 (8.6)
Pancreatitis	4 (5.6)	5 (5.6)	0*	1 (2.9)*
Renal cyst	4 (5.6)	4 (5.6)	0	0
Decreased appetite	2 (2.8)	6 (6.7)	0	0
Urinary tract infection	2 (2.8)	2 (2.2)	6 (21.4)	6 (17.1)
Vomiting	2 (2.8)	3 (3.3)	5 (17.9)	5 (14.3)
Injection site hematoma	0	0	5 (17.9)	5 (14.3)
Injection site urticaria	1 (1.4)	1 (1.1)	4 (14.3)	4 (11.4)
Lymphadenopathy	0	0	4 (14.3)	4 (11.4)
Sinusitis	3 (4.2)	4 (4.4)	4 (14.3)	4 (11.4)
Muscle spasms	2 (2.8)	3 (3.3)	3 (10.7)	4 (11.4)
Myalgia	0	0	3 (10.7)	3 (8.6)
Anxiety	1 (1.4)	3 (3.3)	3 (10.7)	3 (8.6)
Back pain	3 (4.2)	3 (3.3)	2 (7.1)	2 (5.7)
Blood pressure increased	0	0	2 (7.1)	3 (8.6)
Chest pain	2 (2.8)	2 (2.2)	2 (7.1)	2 (5.7)
Cough	3 (4.2)	3 (3.3)	2 (7.1)	2 (5.7)
Increased appetite	0	0	2 (7.1)	2 (5.7)
Loss of consciousness	0	0	2 (7.1)	2 (5.7)
Musculoskeletal pain	1 (1.4)	1 (1.1)	2 (7.1)	2 (5.7)
Neuropathy peripheral	0	0	2 (7.1)	2 (5.7)
Vertigo	0	0	2 (7.1)	4 (11.4)
Viral infection	0	0	2 (7.1)	3 (8.6)

*Does not include 1 patient with “pancreatitis acute”

Source: Clinical Safety Update, SDS 3.2.1.1; Clinical Safety Update, SDS 3.2.1; 4-Month Safety Update SDS 3.2.9; 4-Month Safety Update, SDS 3.2.1

Hypoglycemia is the most frequent adverse event in the NIH trial, and one of the most common in the FHA101 trial. This event is discussed in more detail in Section 7.3.5, Submission Specific Primary Safety Concerns.

All events of fatigue in the patients from the NIH trial were deemed of mild-to-moderate severity. Fatigue did not appear to be related to hypoglycemia, since only one patient (90116) who had an event of fatigue also had hypoglycemia (which occurred three months before the event of fatigue). Of note, fatigue was reported in the medical history of six (8.3%) of 72 patients.

In the NIH trial, nausea events were deemed mild or moderate intensity except for one event of severe intensity. Of eight nausea events, five had a duration from one to 11 days, and six had resolved by the data cutoff date for this submission (data on duration for three events and on resolution for two events are incomplete). None of the events of nausea occurred at the same time as an event of pancreatitis or an event related to the hepatobiliary system. In the FHA101 trial, nausea events were deemed to be of mild or moderate intensity except for one event of severe intensity, reported as a serious adverse event (along with severe vomiting and severe abdominal pain, Patient 677002, see Section 7.3.2, Serious Adverse Events). Of note, four (16%) of 25 patients with medical history captured in the FHA101 trial had a medical history of nausea.

Of 72 patients, six (8.3%) patients in the NIH trials experienced weight loss deemed by the investigator as an adverse event. [There was a mean (± SE) decrease in body weight of -2.0 (± 0.64) kg in patients with data at Year 1 of metreleptin treatment (n=49), with body weight generally remaining stable after the first year for the patients with data up to Year 6.] All six patients with adverse events of weight loss had generalized lipodystrophy. The following table summarizes baseline and last available body weight and BMI for these six patients, as well as the time to onset and metreleptin dose.

Table 74. Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to Weight Loss, NIH Trials

Patient ID / Demog	Metreleptin Dose During Study	Measurements BW (kg)/BMI (kg/m^2)	TEAE [1] (SOC)	Time to Onset (Days)
90116 47 yr F, CGL	0.55 mg BID BL to 6.00 mg QD at Y9 (data cut off)	BW: 60.4 BL; 52.8 Y5 BMI: 22.9 BL; 20.6 Y5	Weight loss	243[2]
90120 23 yr F, CGL	0.80 mg BID BL to 5.50 mg QD at Y8 (data cut off)	BW: 80.6 BL, 53.8 Y6 BMI: 25.2 BL, 17.6 Y6	Weight loss	[3]
90128 15 yr M, AGL	0.2 mg BID BL to 2.50 mg BID at Y7 (data cut off)	BW: 59.1 BL, 52.0 M30 BMI: 21.6 BL, 18.7 M30	Weight loss	270
90150 11 yr M, AGL	2.75 mg QD BL to 3.20 QD at Y3 (data cut off)	BW: 46.3 BL; 46.7 M18; 53.7 M30. BMI: 20.0 BL; 18.4 M18, 19.9 M30;	Weight loss	1
90153 16 yr F, CGL	3.00 mg BID BL to 6.00 mg QD at Y2 (data cut off)	BW: 52.7 BL; 53.7 M4; 48.3 M18. BMI: 20.4 BL; 20.9 M4; 19.2 M18	Decreased appetite Weight loss	176[2] 176[2]
90162 11 yr F, AGL	2.90 mg QD BL to 4.20 mg QD at Y1 (data cut off)	BW: 36.8 BL; 38.2 M12; 33.6 M18. BMI: 14.4 BL; 14.4 M12; 12.5 M18	Decreased appetite Weight loss	216[2] 421

Yr = years; F = female; M = male; BL = baseline; BW = body weight; BMI = body mass index; QD = once daily; BID = twice daily; CGL = congenital generalized lipodystrophy; AGL = acquired generalized lipodystrophy; TEAE = treatment-emergent adverse event; SOC = system organ class.
Notes: Shaded rows indicate TEAEs that occurred between 31 July 2009 and 11 July 2011.
- Last body weight/BMI measurements reflect last available data.
[1] Verbatim.
[2] Start day unknown, calculation based on the 1st of the month and year.
[3] Onset date for the event is unknown; the event occurred in the same month the patient started metreleptin treatment.

Source: Clinical Safety Update, Table 18

Reviewer comment: Because weight loss could be considered a pharmacodynamic effect of the drug, I reviewed the efficacy (HbA1c and TG) findings in these patients, close to the onset of the weight loss adverse event, where known:

- ***Patient 90116: No improvement in HbA1c (7% to 7.2%) although insulin was discontinued; decrease in TG (1543 mg/dL to 160 mg/dL)***
- ***Patient 90120: Lowering of HbA1c and TG decreased by Month 4 and sustained (Month 12: HbA1c 8.7% to 4.5%, off insulin; TG 702 mg/dL to 109 mg/dL)***
- ***Patient 90128: Lowering of HbA1c and TG seen at Month 8 (approximate time of weight loss adverse event); however, he was reportedly only 50% compliant with metreleptin at that time (HbA1c 10.1% to 8.7%; TG 150 mg/dL to 96 mg/dL)***

- ***Patient 90150: No improvements [treatment still ongoing, but notably no baseline diabetes mellitus or hypertriglyceridemia (HbA1c 5% to 5.6% at Month 12; TG 141 mg/dL to 153 mg/dL at Month 12)]***

- ***Patient 90153: Lowering of HbA1c and TG was seen at Month 4 (approximate time of weight loss adverse event): HbA1c 11% to 7.8%; TG 872 mg/dL to 73 mg/dL***

- ***Patient 90162: Lowering of HbA1c and TG was seen at Month 12 (approximate time of weight loss adverse event); however, metformin was also started: HbA1c 7.8% to 5.6%, TG 337 mg/dL to 107 mg/dL***

In summary, weight loss may be associated with improvements in HbA1c and TG; however, this finding is variable.

Urinary tract infection (UTI) was the third most common adverse event in the FHA101 trial (21.4%), although it was not a frequent event in the NIH trials (2.8%). Of note, five (20%) of the 25 patients with medical history captured in the FHA101 trial had a medical history of UTI.

Patients Treated for Obesity

The following table summarizes frequent (incidence 5% or greater in any treatment group) adverse events from the three trials in obese patients and two trials in obese patients with type 2 diabetes in the ISS. The most frequently reported adverse event was injection site reaction, which occurred in 59.8% of metreleptin-treated patients versus 44.7% of placebo-treated patients. The next most frequently occurring adverse events (incidence greater than 10%) were headache (15.7% metreleptin versus 12.3% placebo) and nasopharyngitis (12.1% versus 12.5%).

Table 75. Frequent (Incidence 5% or Greater in Any Treatment) Adverse Events by Preferred Term in Obese Patients, ISS

	Placebo N=351	**Metreleptin N=784**
Any Adverse Event	299 (85.2)	724 (92.3)
Injection site reaction	157 (44.7)	469 (59.8)
Headache	43 (12.3)	123 (15.7)
Nasopharyngitis	44 (12.5)	95 (12.1)
Injection site erythema	2 (0.6)	85 (10.8)
Injection site pruritus	6 (1.7)	63 (8.0)
Fatigue	24 (6.8)	50 (6.4)
Influenza	24 (6.8)	48 (6.1)
Diarrhea	17 (4.8)	42 (5.4)
Nausea	17 (4.8)	42 (5.4)

Injection site inflammation	2 (0.6)	38 (4.8)
Injection site hemorrhage	17 (4.8)	31 (4.0)
Sinusitis	17 (4.8)	30 (3.8)
Back pain	16 (4.6)	29 (3.7)
Oropharyngeal pain	16 (4.6)	29 (3.7)
Hypoglycemia	5 (1.4)	28 (3.6)
Upper respiratory tract infection	26 (7.4)	27 (3.4)
Injection site rash	0	19 (2.4)
Injection site edema	0	18 (2.3)
Urinary tract infection	9 (2.6)	9 (1.1)

Source: ISS, Table 6

Common adverse events were not summarized in the BLA submission for (1) the Amgen obesity trials not included in the ISS, (2) the Amylin obesity trials from the metreleptin-pramlintide development program, (3) the investigator-initiated metreleptin trials, nor (4) compassionate-use programs. The study report for the completed Amylin Phase 2 trial evaluating metreleptin + pramlintide indicates that injection site reactions were the most common adverse events in the metreleptin-only (5 mg) arm.

7.4.2 Laboratory Findings

Changes in ALT and AST, and BUN, serum creatinine, and 24h urine protein are discussed in the relevant subsections of Section 7.3.5, Submission Specific Primary Safety Concerns (Liver Findings and Nephropathy, respectively).

The only other mean change in safety laboratory parameters of note was a moderate decrease from baseline in alkaline phosphatase seen in the NIH trials. Alkaline phosphatase (total and bone-specific) have been shown to be positively correlated with measures of insulin resistance;[37] therefore the decrease may be consistent with the overall improvement in insulin sensitivity in this trial.

7.4.3 Vital Signs

Blood pressure and heart rate changes are reported in Section 7.3.5, Submission Specific Primary Safety Concerns (Cardiovascular-Related Adverse Events).

7.4.4 Electrocardiograms

A thorough QT/QTc study was not conducted in this development program. Electrocardiograms (ECGs) were collected in the metreleptin-pramlintide for obesity development program. In the DFA102 trial, which examined the effect on body weight of various doses of metreleptin and pramlintide administered alone or in combination, there were no clinically significant changes or trends from enrollment in ECG tracings, including QT/QTc interval, in any treatment group during the trial.

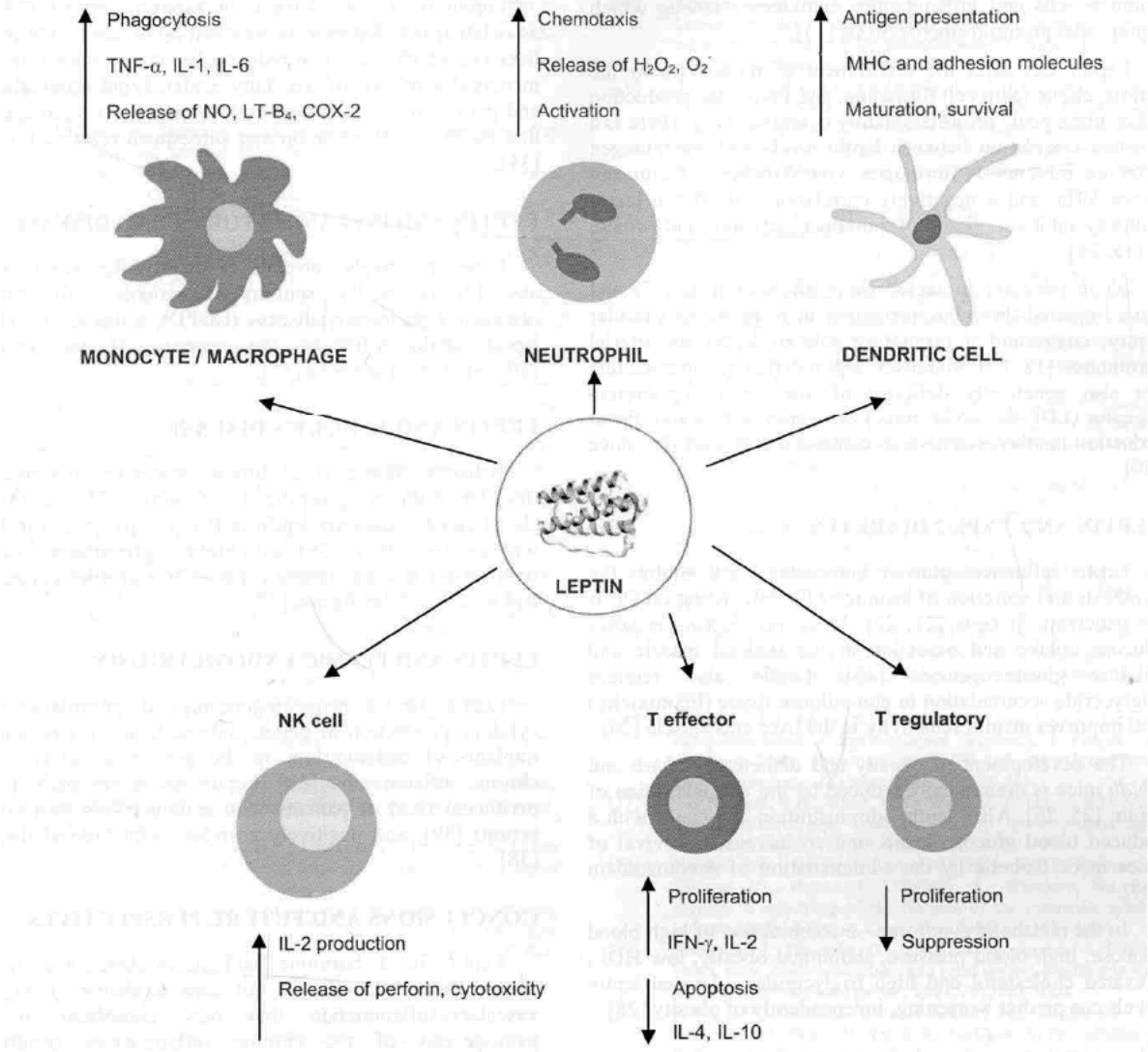
7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

The potential for immunogenicity with metreleptin is high. This is due to drug product-related factors, such as aggregate formation, non-physiological pH, route of administration (subcutaneous), and dosing frequency (daily). In addition, other factors, such as leptin's role in inflammation, as well as patient-related factors may contribute to its immunogenic potential. Leptin activates a number of cell signaling pathways important in T-cell activity and as shown in the figure below, leptin is permissive in cellular proliferation and cytokine production.

Figure 27. Schematic Representation of Leptin Proinflammatory Activities on Immune Cell Subsets



Source: Reference 38

Binding Antibodies

Almost all patients treated with metreleptin develop binding antibodies. In the NIH trials, 86% of patients, FHA101 trial 96% of patients, in the five trials in the Amgen obesity ISS 85% of patients (using a different assay), and in the Amylin obesity (pramlintide-metreleptin) program, 96-100% of patients developed binding antibodies to metreleptin. Development of antibodies appears to result in increased total leptin concentrations to supraphysiologic levels (e.g., greater than 100 ng/mL, and in some cases up to 1000 ng/mL), likely due to delayed clearance of metreleptin bound to antibody and/or assay

interference. The most frequent adverse event associated with development of antibodies to metreleptin / increased antibody titer was inflammatory injection site adverse events.

Reviewer comment: In assessing adverse events that might be associated with development of antibodies, note that almost all patients exposed to metreleptin develop antibodies, and in addition, injection site reactions are a common adverse event associated with metreleptin use. Therefore, the association would be expected.

NIH Trials

Forty-three patients from the 72-patient NIH trials had antibody data available at the time of the BLA submission. Of these, the majority were female (88%) and white (58%); 29 (67%) were pediatric patients (less than 18 years of age), of whom 13 patients were aged 12 years or younger (the youngest patient was 2 years old). Thirty (70%) patients had generalized lipodystrophy (22 congenital and eight acquired) and 13 (30%) patients had partial lipodystrophy (11 familial and two acquired). Mean baseline HbA1c, fasting glucose, and triglyceride concentrations were similarly elevated for the 43 patients with antibody data, as for the 72 patients overall. Mean (± SD) baseline fasting leptin concentration for the 43 patients was 2.1 ± 2.1 ng/mL, consistent with that observed for the 72 patients overall.

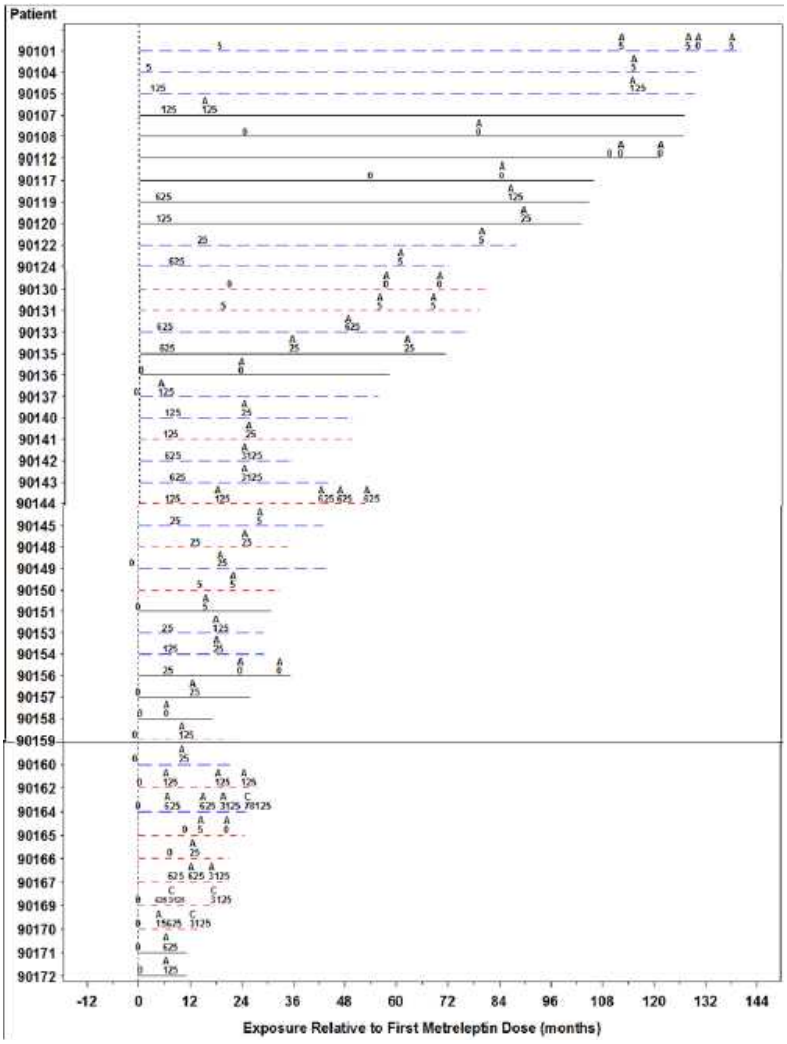
As noted by the sponsor, assessment of antibody status in the NIH trials was not performed in a systematic fashion. The sparse antibody assessments in combination with the varied exposure among patients provide suboptimal data, and results should be interpreted with caution. In patients with large intervals between antibody assessments, the peak (maximum) titer may not have been captured.

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 one month (Patient 90105) to 42 months (Patient 90144) following initiation of metreleptin for the time points at which samples were analyzed.

Most patients who developed binding antibodies to metreleptin continued to maintain an antibody titer on treatment. Antibody titer increased in seven patients (90142, 90143, 90144, 90153, 90164, 90167, and 90169). Other patients had stable or decreased antibody titer over time, despite continuing exposure to metreleptin. In one patient (90156) who initially developed an antibody titer, antibody was no longer observed despite continuing on metreleptin. Six patients (90108, 90112, 90117, 90130, 90136, and 90158) had no evidence of binding antibodies to metreleptin during treatment at the time points assessed. Exposure for these patients up to their last antibody measurement ranged from six months to 121 months. Seven patients (90149, 90151,

90157, 90159, 90160, 90171, and 90172) had only one post-baseline antibody assessment, and thus no determination could be made as to whether antibody titer was increasing or decreasing.

Figure 28. Titers of Binding Antibodies to Metreleptin and Neutralizing Activity Category†††††††††† During Metreleptin Treatment; NIH Trials (N = 43)



Horizontal line represents metreleptin treatment duration as of a data cutoff of 11 Jul 11.
Line styles indicate patient age group at enrollment: short dotted line for ≤ 12 years old, long dotted line for >12 and <18 years old, and solid line for ≥ 18 years old
Numbered data points indicate the titers of binding antibodies, where 0 indicates the absence of binding antibodies at the minimum dilution used and letter data points (A, B, C) indicate category of metreleptin neutralizing activity.
Source: Clinical Addendum, Figure 9

†††††††††† Note that the sponsor has categorized neutralizing activity with an *in vitro* assay from A to E, with A representing no neutralizing activity, and E representing the most potent. The classification is being used in this review for descriptive purposes. See the description in the neutralizing antibodies section, below.

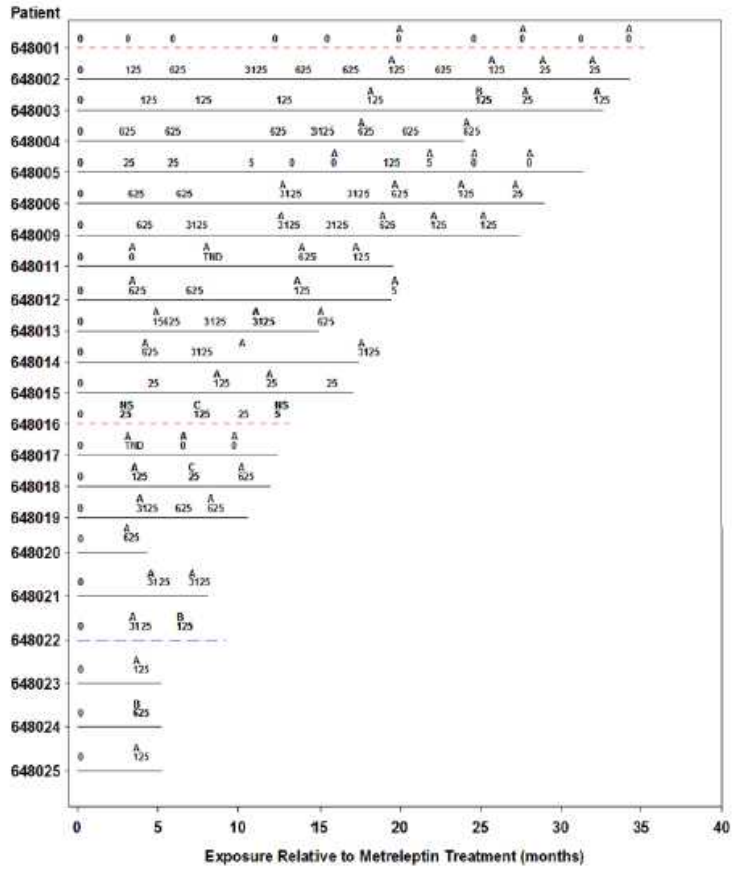
Trial FHA101

Of the 22 out of 28 patients with antibody data, the majority were female (91%) and white (73%); three were pediatric patients (less than 18 years of age), of whom two patients were aged 12 years or younger (the youngest patient was nine years old) at enrollment. Three (14%) patients were diagnosed with AGL and 19 (86%) patients were diagnosed with partial lipodystrophy (18 familial and one acquired). The majority of patients had HbA1c 6% or greater (n = 18, 82%), FPG 126 mg/dL or greater (14, 64%), or fasting TG 200 mg/dL or greater (15, 68%). Mean (±SD) fasting leptin concentration at baseline was 12.9 (± 10.7) ng/mL, with a maximum value of 42.9 ng/mL and with three patients (648001, 648016, and 648022) having leptin concentrations below the lower limit of quantification (less than 0.7 ng/mL).

Of the 22 patients with antibody data, 21 developed detectable binding antibodies following exposure to metreleptin, with titers ranging from 5 to 15625. One patient (648001, a 9-year-old female with AGL) had no evidence of antibodies to metreleptin over approximately 35 months of treatment. Of note, this patient had juvenile dermatomyositis treated with methotrexate; it is unknown if methotrexate treatment could have played a role in the lack of antibody response.

Of the 21 patients who developed binding antibodies to metreleptin, 15 patients continued to maintain an antibody titer on treatment, but the antibody titer tended to decrease over time in the majority of patients, despite continued exposure to metreleptin. In two patients (648005, 648017), antibody was no longer observed despite continued exposure to metreleptin. Four patients (648020, 648023, 648024, and 648025) had only one antibody assessment after baseline due to the timing of the data cut relative to initiation of metreleptin treatment.

Figure 29. Titers of Binding Antibodies to Metreleptin and Neutralizing Activity Category†††††††††† During Metreleptin Treatment; FHA101, N = 22



TND = titer not determined (but sample confirmed positive for binding antibodies); NS = non-specific.
Horizontal line represents metreleptin treatment duration as of a data cutoff of 07 Mar 2012.
Line styles indicate patient age group at enrollment: short dotted line for ≤ 12 years old, long dotted line for >12 and <18 years old, and solid line for ≥ 18 years old.
Numbered data points indicate the titers of binding antibodies, where 0 indicates the absence of binding antibodies at the minimum dilution used, and letter data points (A, B, C) indicate category of metreleptin neutralizing activity.

Neutralizing Antibodies

In both the NIH and FHA101 trials, all samples assessed for neutralizing activity were assayed in parallel to the binding antibody testing. Each test sample was categorized based on the potency and specificity of neutralizing activity. Potency was determined by successive dilution of samples for which test results were greater than the method-defined threshold inhibition value. Specificity was determined by assessing the effect of test sample addition on murine interleukin-3 (mIL-3)-dependent cell metabolism.

The following summarizes the categorization approach for neutralizing activity results with the sponsor's *in vitro* neutralizing activity assay:

- Category A: result is less than the assay cut-point on initial testing
- Category B: result is higher than the assay cut-point on initial testing, but is less than the assay cut-point on repeat testing
- Category C: result is higher than the assay cut-point on initial testing and re-testing, but is less than the assay cut-point after additional 1:10 dilution
- Category D: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 dilution but not after 1:100 dilution
- Category E: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 dilution and 1:100 dilution

Patients Treated for Lipodystrophy

Three patients (90164, 90169, and 90170) from the NIH trials, all pediatric, have had neutralizing activity at the following time points: Patient 90164 at Years 2 and 3, Patient 90169 at Months 8 and 18, and Patient 90170 at Month 12. Two patients (648016 and 648018) from the FHA101 trial had neutralizing activity after approximately six months of treatment. One additional case from FHA101 was reported in the four-month safety update. This patient (648019), who had previously negative neutralizing assay (Category A) results, had a Category C result at a subsequent assessment at Month 18. Narratives for these six cases are presented below. All other patients tested from the NIH or FHA101 trials have had no evidence of neutralizing activity to date.

Post-review addendum: Category E results were obtained from Patient 90143 after a review of available samples from patients reported to have sepsis. The case report is presented below.

Patient 90164: At the time of the event, this was a 19-year-old female with CGL. This patient initiated therapy with metreleptin on 17 Mar 2010 at the age of 16. Her medical history included cirrhosis, hepatosplenomegaly, chronic gastritis, grade III esophageal varices, IgA nephropathy, proteinuria, diabetes with extreme insulin resistance, hypertriglyceridemia, hypertension, hirsutism, and amenorrhea. Concomitant medications at baseline included U-500 insulin and metformin. At baseline prior to initiation of metreleptin, plasma leptin concentration was 0.7 ng/mL, HbA1c was 9.8%, and serum TG was 600 mg/dL. See follow-up labs in the table below:

Table 76. Patient 90164: Available Antibody Status and Efficacy Labs Through Year 3

Date	Antibody titer	Neutralizing activity category	Leptin concentration (ng/mL)	HbA1c (%)	TG (mg/dL)
Mar 2010 (baseline)	NA	NA	0.7	9.8	600
Sep 2010	625	A	152.4	6.9	231
May 2011 (Yr 1)	625	A	318.3	6.7	168
Oct 2011	3125	A	NA	5.9	226
Apr 2012 (Yr 2)	78125	C	42.2	8.7	263
Aug 2013 (Yr 3)	NA	E	NA	7.4	674

The patient was hospitalized in (b) (6) for sepsis related to *Gemella* species (of note, hospital course was complicated by *Clostridium difficile* colitis) and again on (b) (6) (b) (6), for sepsis related to *Streptococcus viridans*, treated with a four-week course of IV ceftriaxone. She was unable to return to the NIH for her Year 3 scheduled visit in (b) (6) (b) (6) due to her hospitalization for sepsis. As a result, arrangements were made for a plasma sample to be collected by her local physician for antibody assessment. The sponsor was notified on 8 Aug 2013 that this plasma sample was tested for neutralizing activity category E (high potency activity). Binding antibody assessment is still pending at the time of this writing. No clinical laboratory tests were done at this visit. The patient is scheduled for a follow-up visit with her local physician on 20 Aug 2013. [Supplemental information received 26 Aug 2013 reported non-fasting lipids and laboratory results from 20 Aug 2013 which included: total cholesterol 269 mg/dL, HDL-cholesterol 25 mg/dL, non-HDL-C 244 mg/dL, cholesterol / HDL ratio 10.8, LDL-C 152 mg/dL, TG 674 mg/dL, HbA1c 7.4%.] As of 18 Sep 2013, the patient remained on metreleptin. In Oct 2013, an event of malignant otitis externa with *Stenotrophomonas maltophilia* bacteremia for which the patient was hospitalized in (b) (6) was reported. FDA received safety reports of two additional hosptializations for bacterial infections under the NIH trial IND. The patient was admitted on (b) (6) for fever (104.1°F). Blood cultures grew *S. viridans*. The patient was treated with IV nafcillin then switched to ceftriaxone for six weeks via peripherally inserted central catheter (PICC). Most recently, the patient was sent to the local hospital by her primary physician for positive blood cultures with *Acinetobacter baumanii* (collected (b) (6)). The patient had complained of feeling weak and sick and febrile for three days prior and experienced rigors the night before her hospital admission (temperature was 101°F). The patient was started on meropenem and the PICC line (still in place from the previous infection treatment) was removed. The patient also complained of abdominal pain, which was thought due to C. diff. colitis. The patient was discharged home (b) (6) on oral ciprofloxacin for acetinobacter bacteremia and oral vancomycin for C. diff.

Reviewer comment: This case is confounded by the patient's medical history that could compromise the immune system and predispose to infections (diabetes, cirrhosis) and complicated by repeated hospitalizations, catheters, and antibiotics. While some of the organisms could be oral flora, and poor dentition

was reported in the notes from the hospital, S. maltophilia can cause nosocomial infections in immunocompromised patients.[39] It is also notable that no source for her initial infections was found (e.g., no evidence for endocarditis on echocardiogram). Whether neutralizing antibodies to leptin could play a role in the development of the numerous bacterial infections is unknown. With respect to the potential for loss of efficacy, it is noted that HbA1c and TG increased after Year 1. A blood glucose value reported in the most recent post-hospitalization doctor's note (finishing 14-day course of levofloxacin, but not reported to be actively infected) was 354 (units not provided). She was also reported to have hepatomegaly at that visit; it is unknown if this had improved at some point initially on metreleptin.

Patient 90143 [*information available post-review*]: On 10 Jan 2014, the sponsor received results from testing for neutralizing activity in a sample from an 18-year-old female patient with CGL that showed evidence of neutralizing activity to metreleptin. Study therapy was initiated on 27 Sep 2007. The patient has a medical history of CGL, insulin resistance diabetes mellitus, cirrhosis of the liver with portal hypertension, hepatopulmonary syndrome, arthritis of the knees, joint contractures, chronic hypoxia, primary amenorrhea, intrapulmonary vascular dilations, increased anxiety, and osteopenia. Baseline laboratory assessments in Sep 2007 included: HbA1c 8.6%, FPG 147 mg/dL, TG 49 mg/dL, ALT 42 U/L, and AST 39 U/L.

On 29 Apr 2008, laboratory results included HbA1c 5%, FPG 110 mg/mL, ALT 40 U/L, AST 46 U/L. Antibody testing showed binding antibody titer 625 (neutralizing activity was not assessed).

On 16 Sep 2009, laboratory testing showed HbA1c 5.8%, FPG 83 mg/mL, TG 43 mg/mL, ALT 33 U/L, and AST 34 U/L, binding antibody titer 3125 and no evidence of neutralizing activity (category A result).

On 11 May 2011, laboratory testing showed HbA1c 13.1%, FPG 230 mg/mL, TG 55 mg/mL, ALT 52 U/L, and AST 47 U/L. No assessment of antibody status or neutralizing activity was available for this visit.

In (b) (6) (approximately 4 years after initiation of metreleptin therapy), the patient was hospitalized at a local hospital in (b) (6) with a diagnosis of sepsis. The source of infection was not found during hospital admission. No medical records are available for this event. The patient was treated with antibiotics along with a BRAT (bananas, rice, applesauce, toast) diet and the event resolved. All information is based on a report from the mother (who is a nurse) to the NIH investigators. At the time of the sepsis event, the patient did not have an assessment for antibody status or neutralizing activity to metreleptin.

On 8 Jan 2013, laboratory testing showed HbA1c 11.2%, FPG 217 mg/mL, TG 79 mg/mL, ALT 63 U/L, and AST 43 U/L.

The patient has not returned to the NIH for follow-up assessment since the 8 Jan 2013 visit. Testing for neutralizing activity on the patient's last available sample (from 8 Jan 2013) was initiated in Dec 2013 during review of sepsis events in all patients treated with metreleptin, including the first case of category E neutralizing activity reported in the NIH study in a patient who had multiple episodes of sepsis while receiving metreleptin treatment (Patient 90164).

The sponsor received notification on 10 Jan 2014 that the sample from 8 Jan 2013 had evidence of high potency, reproducible neutralizing activity (Category E result).

Reviewer comment: It is unknown whether the sepsis episode can be associated with neutralizing antibodies, since antibody testing was not available at the time of the event. However, the patient does appear to have experienced loss of glycemic efficacy since 2011. Category E neutralizing antibodies were identified from a sample dated Jan 2013.

Patient 90169: This was a 4-year-old female with CGL at study entry. Antibody titer was negative at baseline (pre-dose), 625 at Month 4 (neutralizing activity not assessed), and 3125 at Months 7 and 17 (both with positive neutralizing activity, category C). Plasma leptin concentration was 0.7 ng/mL at baseline and increased to 12.3, 17.5, and 27.0 ng/mL at Months 4, 7, and 17, respectively. HbA1c increased from 8.7% at baseline to 10.5%, 10.0%, and 9.2% at Months 4, 7, and 17, respectively. Serum TG concentrations remained relatively stable during treatment (370 mg/dL, 322 mg/dL, 377 mg/dL, and 325 mg/dL at baseline, Months 4, 7, and 17, respectively). No adverse events were reported for this patient. This patient appeared to be a non-responder to metreleptin treatment. Per the study investigators, compliance was an issue in this 4-year-old patient, and the assessment by the site was that the patient actually received only a small percentage of prescribed therapy during the initial seven months, after which compliance improved but may still have been below 70%. In the four-month safety update, results from Month 24 were reported: antibody titer was 625 and neutralizing activity was negative (Category A). Leptin concentration was 58.7 ng/mL. The patient's metabolic control improved, with HbA1c decreased from 9.2% to 6.5% and TG decreased from 325 mg/dL to 224 mg/dL.

Patient 90170: This was an 11-year-old female with AGL at study entry. Antibody titer was negative at baseline (pre-dose), 15625 at Month 4 with negative neutralizing activity (Category A), and 3125 at Month 12 with positive neutralizing activity (Category C). Plasma leptin concentration was 1.0 ng/mL at baseline and increased to 72.3 ng/mL and 81.3 ng/mL at Months 4 and 12, respectively. HbA1c was in the normal range at baseline (5.3%) and remained stable during treatment. Serum TG concentrations were 368 mg/dL at baseline, 113 mg/dL at Month 4, and 253 mg/dL at

Month 12. One adverse event of peripheral edema was reported for this patient 345 days after initiation of metreleptin. After the data cutoffs used for this document, a serious adverse event of anaplastic large cell lymphoma was reported for this patient (see Section 7.6.1, Human Carcinogenicity). At the time of the serious adverse event for anaplastic large cell lymphoma, the sponsor assessed the binding titer and neutralizing activity (Month 24), and this was reported in the four-month safety update. The patient's binding titer and neutralizing activity remained 3125 and positive (Category C), respectively. Leptin concentration (112.2 ng/mL) and glycemic control (HbA1c 4.9%) remained constant; and TG modestly increased to 363 mg/dL. The patient discontinued metreleptin treatment on 25 Dec 2012, a few weeks after diagnosis of the anaplastic large cell lymphoma, but later reinitiated metreleptin treatment (12 Feb 2013).

Patient 648016: This was an 11-year-old male with AGL at study entry, who initiated metreleptin based on inclusion criteria of hypertriglyceridemia as well as a history of diabetes, although glycemic control was good at the time of starting metreleptin treatment (HbA1c 5.5%). Other considerations for initiating metreleptin therapy in this patient were chronic active autoimmune hepatitis (with severely elevated liver function tests), and aggressive behavior related to difficult to control hyperphagia (information reportedly on file at Amylin). Maximum binding antibody titer was 125 with positive neutralizing activity (Category C) at Month 6. Titer decreased to 5 at Month 12 (non-specific result for neutralizing activity), and was 25 at Months 15, 21, and 24 without neutralizing activity (Category A). Fasting leptin concentration was less than 0.7 ng/mL at baseline, increased to 3.6 ng/mL at Month 6, and decreased to 1.7 ng/mL at Month 12. HbA1c was normal at baseline (5.5%) and through Month 24 (4.6%). TG values were: 354 mg/dL at baseline, then 42 mg/dL, 469 mg/dL, 30 mg/dL, 41, 63, 196, and 66 mg/dL at Months 3, 6, 12, 15, 18, 21, and 24, respectively. AST and ALT decreased from 208 IU/L and 419 IU/L at baseline, respectively, through Month 24.

Patient 648018: This was a 40-year-old female with APL at study entry. Binding antibody titer was 125 at Month 3, 25 at Month 7 (Category C neutralizing activity), 625 at Month 10 (Category A neutralizing activity), and 125 at Month 18 (Category A neutralizing activity). Leptin concentration increased from 8.4 ng/mL at baseline to 20.7 ng/mL at Month 3, 40.7 ng/mL at Month 7, and 68.6 ng/mL at Month 10. HbA1c was normal (5.7%) at baseline and remained stable through Month 18 (5.7%). TG at baseline was 1243 mg/dL, then 471 mg/dL, 1435 mg/dL, and 597 mg/dL at Months 10, 15, and 18, respectively.

Patient 648019: This was a 55-year-old female with FPL at study entry. Binding antibody titer was 3125 at Month 3 (Category A neutralizing activity), 625 at Months 6 and 9 (Category A neutralizing activity at Month 9), 3125 at Months 12 and 15 (Category A neutralizing activity at Month 15), and 625 at Month 18 (Category C neutralizing activity). Leptin concentration increased from 2.7 ng/mL at baseline to 116.6 ng/mL at Month 3, 17.5 ng/mL at Month 6, and 27.7 ng/mL at Month 9. HbA1c

was normal (5.6%) at baseline and remained stable through Month 18 (5.7%). TG was 79 mg/dL at baseline, and 121, 114, 131, 150, and 120 mg/dL at Month 6, 9, 12, 15, and 18, respectively.

Patients Treated for Obesity

No patients in the Amgen obesity trials were known to have developed neutralizing antibodies.‡‡‡‡‡‡‡‡‡‡

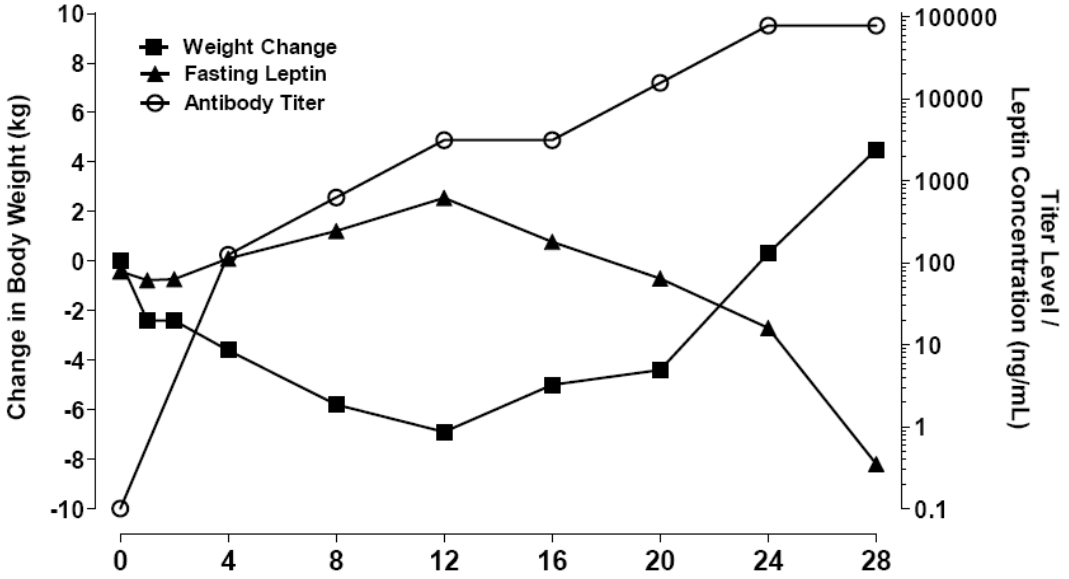
In the combined Phase 2 metreleptin-pramlintide trials, three patients out of 579 who were exposed to metreleptin have been identified with Category D or E antibodies, which indicate high potency neutralizing activity to metreleptin.

All three patients were enrolled in DFA102 and were characterized by: (a) high titer of binding-antibody to metreleptin; (b) plasma leptin concentration near or below the lower limit of the immunoassay sensitivity; and (c) weight regain following initial weight loss during the trial. On the basis of these findings, the first two identified patients were recalled to the study sites in November and December 2009 for additional clinical history and collection of samples for leptin and antibody assays. These tests suggested the presence of neutralizing activity against metreleptin in serum samples at the end of the 28-week study (present starting at ~20 to 24 weeks) as well as at the follow-up assessment (which occurred approximately 8 and 12 months after study termination).

- Patient 120011 was a 40-year-old white female randomized to metreleptin 5 mg (placebo + metreleptin). She had a baseline BMI of 42.5 kg/m^2 and a baseline body weight of 129.9 kg. During the trial, the patient experienced adverse events of injection site erythema, injection site pruritus, elevated ALT, injection site nodule, and injection site hemorrhage. Concomitant medications taken during the study included melatonin for insomnia, calamine lotion for injection site pruritus, and Zyrtec for injection site erythema and pruritus. At study termination on 25 Mar 2009, the patient weighed 134.4 kg, a gain of 4.5 kg from baseline. The patient did not enroll into the extension study (DFA102E). Approximately one month after study termination on 28 Apr 2009, the patient was seen by her PCP and weighed 145.5 kg (+15.6 kg from baseline). Over the next several months she continued to gain weight and developed impaired fasting glucose. On 23 Nov 2009, approximately eight months after study termination, the patient was brought back to the study site for follow-up evaluation of the clinical and laboratory findings described above of high binding-antibody titer, low plasma leptin level, and weight regain. At this visit, she weighed 155.9 kg (+26.0 kg from study baseline). Another follow-up visit with the patient was attempted but the patient did not respond to three attempts of contact by the study site. No further information on this patient is available.

‡‡‡‡‡‡‡‡‡‡ Note that the Amgen assay is different from the Amylin assay, and may be less sensitive.

Figure 30. Plasma Leptin Concentration, Metreleptin Binding-Antibody Titer, and Change in Body Weight over Time for Patient 120011 in DFA102

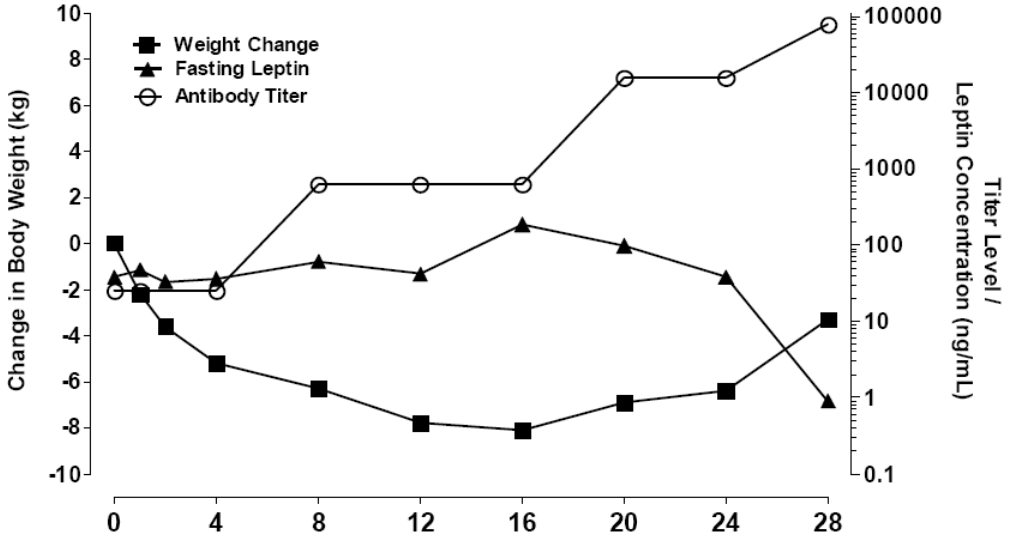


Source: IND 50259 15-day safety report

Reviewer comment: This figure does not reflect the 26 kg from baseline that the patient gained over eight months after study termination.

- Patient 130019 was a 48-year-old white male randomized to pramlintide 180 mcg + metreleptin 2.5 mg. The patient had a baseline BMI of 38.2 kg/m^2 and a baseline body weight of 127.9 kg. During the trial, the patient had an initial weight loss of 6.3% by Week 16 and ended the study with weight loss of 2.6%. At study termination binding antibody titer was maximal (78125) and coincided with low leptin concentrations. During the trial the patient experienced adverse events of diarrhea and stomach discomfort, injection site pruritus, nausea, and a sore throat. The patient did not enroll into the extension study. In April 2009, approximately four months after study termination the patient was diagnosed with type 2 diabetes. On 15 Dec 2009, approximately 12 months after study termination, the patient was brought back to the study site for follow-up evaluation of the clinical and laboratory findings of high binding-antibody titer, low plasma leptin level, and weight regain. At this visit, he weighed 140.5 kg (+12.6 kg from study baseline). On 15 Jan 2010, high antibody titer and low plasma leptin concentrations were again noted. On 07 Oct 2010 the patient did not return for a visit, but reported that his medical history was stable with no significant changes or events or new diagnoses since the last follow-up visit and his weight was 128.2 kg. (Of note, his baseline weight at the start of the DFA102 study was 128 kg; therefore, his self-reported weight appeared to return back to baseline.)

Figure 31. Plasma Leptin Concentration, Metreleptin Binding-Antibody Titer, and Change in Body Weight over Time for Patient 130019 in DFA102



Source: IND 50259 15-day safety report

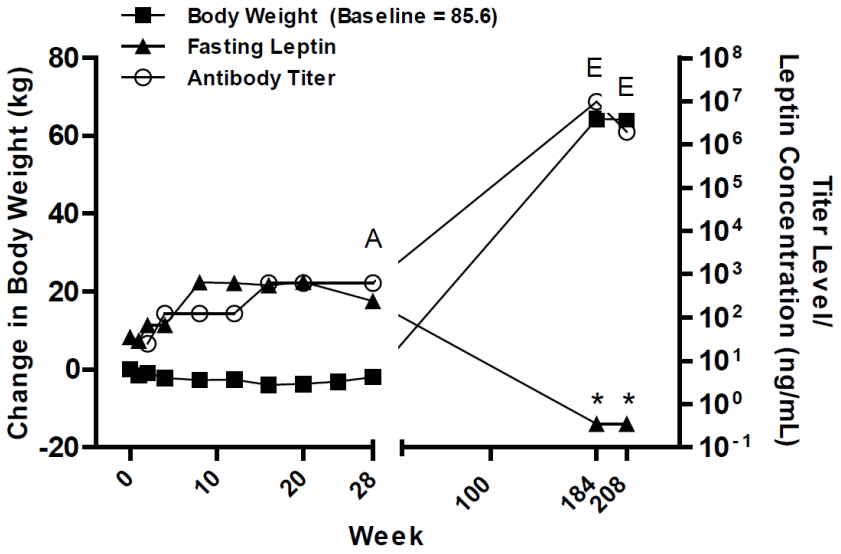
Reviewer comment: This figure does not reflect the 12.6 kg from baseline that the patient gained over 12 months after study termination.

Subsequent to these two submissions a third case of positive neutralizing activity to metreleptin was identified during the testing of plasma samples collected in DFA106. DFA106 was a safety follow-up study under IND 50259 (metreleptin for obesity) designed to acquire long-term follow-up from patients who received at least one dose of study medication during Amylin's obesity development program (trials DFA101, DFA102, and DFA102E). This study was conducted in response to the two patients in study DFA102 who were identified to have developed neutralizing activity to metreleptin and weight gain.

- Patient 139005 was a 39-year-old black female who was randomized to metreleptin 2.5 mg BID plus pramlintide 360 mcg BID in DFA102. Her baseline BMI was 33 kg/m^2 and weight was 85.6 kg. At study termination, her weight was 83.6 kg. The patient's last dose of trial medication was 28 Nov 2008. On Jan 13, 2012, at the follow-up visit for DFA106, additional relevant medical history included abnormal weight gain, shortness of breath, arthralgia, hypopituitarism, peripheral edema, back pain, hyperglycemia, and vitamin D deficiency. She had a plasma sample demonstrating very high anti-leptin binding antibody titer (9,765,625) and no detectable leptin (less than 0.7 ng/mL). The patient's weight on 14 Jan 2012 was 150.0 kg (i.e., weight gain of 66.4 kg since study termination). On 5 Apr 2012, approximately 1225 days after the last dose of study drug, neutralizing activity (category E) to metreleptin was detected in the patient's plasma sampled under

study DFA106. Follow-up weight reported from June 2013 (54 months after study termination) remained unchanged at 150 kg. Metreleptin antibodies titer was 1,953,125 and metreleptin neutralizing activity was category E.

Figure 32. Plasma Leptin Concentration, Metreleptin Binding-Antibody Titer, and Change in Body Weight over Time for Patient 139005 in DFA102 and DFA106



Source: IND 50259 15-day safety report

Potentially Immune-Related Adverse Events

Patients Treated for Lipodystrophy

Metreleptin could, in theory, exacerbate autoimmunity based on the role of leptin in regulating immune function. Autoimmune adverse events are highlighted in other sections of this review. The sponsor identified the following adverse events consistent with autoimmune disease in the NIH trials:

Table 77. Patients with Adverse Events Consistent with Autoimmune Disease, NIH Trials

Patient ID	Age (years) and Gender (M/F)	LD Subtype	Relevant Medical History	Relevant Adverse Events
90107	42 yr F	FPL	No relevant medical history	Lupus anticoagulant
90109	13 yr F	AGL	Type 1 diabetes mellitus	Chronic inflammatory hepatitis, Membranoproliferative glomerulonephritis
90110	8 yr F	AGL	Hashimoto's thyroiditis, Kawasaki's disease, Autoimmune hepatitis, Common variable immunodeficiency	Elevated ALT, Worsening autoimmune hepatitis, Parainfluenza pneumonia, streptococcal pharyngitis, URI, sinusitis, ear infection, flu
90113	12 yr F	CGL	No relevant medical history	Hashimoto's thyroiditis
90114	35 yr M	AGL	Chronic renal failure, Proteinuria	Membranoproliferative glomerulonephritis

Based on Sponsor review of TEAEs.
Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 14

In the NIH trials, 11 (15.3%) of 72 patients experienced 13 events of potentially immune-related adverse events, including the events of urticaria (2.8%), anaphylactic reaction (1.4%), and papular rash (1.4%).

- Patient 90104 was a 17-year-old female with CGL at study entry who experienced pruritus 41 days after initiating metreleptin treatment. The event was treated with loratadine and resolved after 30 days. The patient was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90105 was a 14-year-old female at study entry with CGL who experienced urticaria (verbatim: hives) approximately 2.5 years after initiating metreleptin treatment. The patient discontinued use of metreleptin on her own from 01 Dec 2002 to 15 Mar 2003. The event of urticaria occurred 07 Mar 2003 while she was off metreleptin. She resumed metreleptin on 15 Mar 2003 until 07 Apr 2003. The event of urticaria was treated with cetirizine hydrochloride and hydroxyzine and resolved within a month. The patient was off metreleptin treatment again from 07 Apr 2003 until 29 Oct 2003 due to poor compliance but restarted metreleptin on 29 Oct 2003 and was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90109 was a 13-year-old female at study entry with AGL. The patient experienced papular rash (verbatim term: red, vesicular rash on face, 2-3 papules) approximately 14 months after initiating metreleptin treatment. The event resolved two days later. The patient was withdrawn from the study approximately one month after the event due to "health issues".

- Patient 90110 was an 8-year-old female at study entry with AGL who had a history of asthma and allergic rhinitis. The patient had an adverse event of asthma (verbatim term: asthma exacerbation) about six months after initiating metreleptin treatment and was treated with Seretide. A resolution date for the event was not provided. The patient continued study participation and was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90117 was a 45-year-old female with FPL who experienced an anaphylactic reaction to eating a moldy orange nearly four years after initiating metreleptin treatment. The patient presented to the emergency room with symptoms of hives, shortness of breath, upset stomach, diarrhea, and sore throat and was treated with IV benadryl and with Pepcid but was not hospitalized. The event was assessed by the investigator unrelated to metreleptin (rather, food-related) and resolved on the same day. The patient continued study participation and was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90135 was a 35-year-old female with FPL who experienced urticaria (verbatim: hives) about one month after initiating metreleptin treatment. The event was treated with IV Benadryl and resolved on the same day. The investigators noted that the urticaria was a precursor to the appendectomy that occurred on the same day. The patient continued study participation and was still on metreleptin treatment as of the July 2011 data cutoff date.

Other potentially immune-related but more non-specific events included arthralgia (four patients with one event each), and pruritus, asthma, eyelid edema, and injection-site urticaria (n = 1 for each event). The only adverse event considered related to metreleptin was the injection-site urticaria. None of these potentially immune-related events were considered serious or led to patient withdrawal from the study. All of these events were considered either mild or moderate in intensity except one event of asthma which was severe and occurred in a patient with a medical history of this condition.

In the FHA101 trial, nine (32.1%) of 28 patients experienced 13 events of potentially immune-related adverse events, including events of urticaria, swelling face, rash, pruritus, injection site inflammation, and injection site pruritus (all one patient for each event), and injection site urticaria (four patients with one event each). Further detail on the events of face swelling, urticaria, and rash is provided below.

- Patient 648001 was a 9-year-old female at study entry with AGL. The patient experienced face swelling and erythema approximately two months after initiating metreleptin treatment. The event was treated with clindamycin and resolved after four days. The patient continued study participation and was still on metreleptin treatment as of the March 2012 data cutoff date. The investigator assessment of this event was that it was questionable whether or not the patient had objective facial swelling. The event was not felt to represent a flare of her juvenile dermatomyositis.

The patient was felt to have an upper respiratory infection, and was treated for a possible sinusitis.

- Patient 648016 was an 11-year-old male at study entry with AGL who had a history of intermittent hives (starting about 4.5 years prior to starting metreleptin), which were treated with diphenhydramine. The patient experienced two events of urticaria. Onset of these events was 10 days and almost one year after the first dose of metreleptin. For the first urticaria event, the patient was treated with cetirizine, and the event resolved after 81 days. The metreleptin dose was briefly decreased. For the second urticaria event, the patient was treated with epinephrine, prednisone, ranitidine, and cetirizine, and the event resolved after five days. This patient also experienced rash approximately 3.5 months after initiating metreleptin treatment. The event was not treated and resolved after 19 days. The patient continued study participation and was still on metreleptin treatment as of the March 2012 data cutoff date.

- Patient 648019 was a 55-year-old female at study entry with FPL. The patient experienced pruritus 16 days after the first dose of metreleptin. This patient also had injection site urticaria in the same month as the event of pruritus (exact date not specified). The pruritus was treated with hydrocortisone cream. Both events were assessed by the investigator as related to metreleptin and considered resolved within 1-2 months. The patient continued study participation and was still on metreleptin treatment as of the March 2012 data cutoff date.

Three other patients (648004, 648006, and 648014) had events of injection site urticaria, all with onset 22 days after the first dose of metreleptin. No concomitant medication was given for these events except for Patient 648014 (treated with topical clobetasol). The events resolved after 34, 66, and 15 days, respectively. One patient (648021) had two events of injection site inflammation, the first 20 days after starting metreleptin (treated with Benadryl and topical hydrocortisone) and the second approximately four months after starting metreleptin (not treated). The events resolved after 81 and 15 days, respectively.

Patients Treated for Obesity

In the five obesity trials that comprise the ISS (Amgen) the most common adverse events for metreleptin and placebo patients were injection-site reaction (59.8% versus 44.7%). Severe injection site reactions were noted in seven metreleptin-treated patients versus one placebo-treated patient. In addition to the preferred term ‘injection site reaction’, injection-site adverse events occurring more frequently in metreleptin-treated compared to placebo-treated patients included injection site erythema (10.8% versus 0.6%), injection site inflammation (4.8% versus 0.6%), injection site edema (2.3% versus 0.0%), injection site pruritus (8.0% versus 1.7%), and injection site rash (2.4% versus 0.0%). Non-injection site reaction adverse events reported to be associated with

hypersensitivity were experienced by 14% of metreleptin-treated patients versus 8% of placebo-treated patients; potential eosinophilia-related adverse events (e.g., myalgia, thrombophlebitis) were experienced by 6% of metreleptin-treated patients and 4% of placebo-treated patients. The number of patients experiencing events of anaphylactic reaction, angioedema, potential hypersensitivity-related cutaneous reactions was similar between metreleptin- (6.1%) and placebo- (5.7%) treated patients. The most common such adverse event was rash for both groups (2.4% metreleptin versus 2.8% placebo). There were no cases of Steven-Johnson syndrome or toxic epidermal necrolysis reported in any treatment group.

In the Amgen trials not included in the ISS and the metreleptin + pramlintide for obesity clinical program, the majority of potentially immune-related adverse events were related to injection site reactions. Other adverse events (hypersensitivity, rash, eosinophilia, joint swelling, arthralgias, arthritis) were infrequent. One notable event was a serious adverse event of hypersensitivity in a patient treated with metreleptin in Amylin trial DFA104. See Section 7.3.2, Nonfatal Serious Adverse Events for the narrative.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Because of the small number of patients, the highly individualized dose titration implemented in the lipodystrophy trials, and changes in dosing frequency over time, a dose-response for adverse events could not be assessed. However, the ISS (five pooled Amgen obesity trials) provide some insight into safety findings by dose. In these trials, a total of 1072 obese patients with or without diabetes received metreleptin at doses of 10 mg QD or BID and 20 mg QD or placebo up to 42 weeks. In general, a clear dose-response was not seen for most adverse events. See the tables below for adverse events by dose for patients in the obesity trials with and without diabetes, by system organ class and preferred term, respectively.

Table 78. Incidence of Treatment-Emergent Adverse Events Summarized by System Organ Class, ISS

	Overweight/Obese			Overweight/Obese with T2DM		
	Pbo N=251	**ML 10 mg N=214**	**ML 20 mg N=374**	**Pbo N=100**	**ML 10 mg N=61**	**ML 20 mg N=135**
All Adverse Events	207 (82.5)	192 (89.7)	354 (94.7)	92 (92.0)	53 (86.9)	125 (92.6)
Blood and lymphatic system disorders	0	0	5 (1.3)	0	0	1 (0.7)
Cardiac disorders	1 (0.4)	3 (1.4)	6 (1.6)	0	2 (3.3)	3 (2.2)
Ear and labyrinth disorders	10 (4.0)	1 (0.5)	8 (2.1)	0	1 (1.6)	4 (3.0)
Endocrine disorders	0	0	3 (0.8)	1 (1.0)	0	0
Eye disorders	7 (2.8)	2 (0.9)	10 (2.7)	2 (2.0)	0	4 (3.0)
Gastrointestinal disorders	46 (18.3)	30 (14.0)	82 (21.9)	33 (33.0)	12 (19.7)	25 (18.5)
General disorders and administration site conditions	142 (56.6)	175 (81.8)	332 (88.8)	70 (70.0)	42 (68.9)	105 (77.8)
Hepatobiliary disorders	2 (0.8)	0	0	0	0	0
Immune system disorders	4 (1.6)	3 (1.4)	8 (2.1)	5 (5.0)	2 (3.3)	6 (4.4)
Infections and infestations	92 (36.7)	86 (40.2)	126 (33.7)	40 (40.0)	23 (37.7)	51 (37.8)
Injury, poisoning and procedural complications	28 (11.2)	19 (8.9)	42 (11.2)	12 (12.0)	6 (9.8)	13 (9.6)
Investigations	5 (2.0)	3 (1.4)	7 (1.9)	8 (8.0)	2 (3.3)	6 (4.4)
Metabolism and nutrition disorders	6 (2.4)	1 (0.5)	6 (1.6)	9 (9.0)	10 (16.4)	25 (18.5)
Musculoskeletal and connective tissue disorders	44 (17.5)	36 (16.8)	65 (17.4)	19 (19.0)	10 (16.4)	22 (16.3)
Neoplasms benign, malignant and unspecified	3 (1.2)	3 (1.4)	1 (0.3)	2 (2.0)	0	4 (3.0)
Nervous system disorders	52 (20.7)	49 (22.9)	86 (23.0)	18 (18.0)	14 (23.0)	40 (29.6)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.3)	0	0	0
Psychiatric disorders	10 (4.0)	12 (5.6)	25 (6.7)	11 (11.0)	4 (6.6)	8 (5.9)
Renal and urinary disorders	3 (1.2)	1 (0.5)	1 (0.3)	7 (7.0)	1 (1.6)	5 (3.7)
Reproductive system and breast disorders	13 (5.2)	6 (2.8)	22 (5.9)	6 (6.0)	3 (4.9)	4 (3.0)
Respiratory, thoracic and mediastinal disorders	36 (14.3)	17 (7.9)	56 (15.0)	10 (10.0)	8 (13.1)	15 (11.1)
Skin and subcutaneous tissue disorders	26 (10.4)	22 (10.3)	46 (12.3)	10 (10.0)	6 (9.8)	19 (14.1)
Surgical and medical procedures	4 (1.6)	1 90.5)	2 (0.5)	0	0	1 (0.7)
Vascular disorders	5 (2.0)	8 (3.7)	8 (2.1)	4 (4.0)	1 (1.6)	2 (1.5)

Source: ISS, Supporting Data Summary 5.1

Table 79. Frequent (Incidence 5% or Greater in Any Treatment) Adverse Events by Preferred Term, ISS

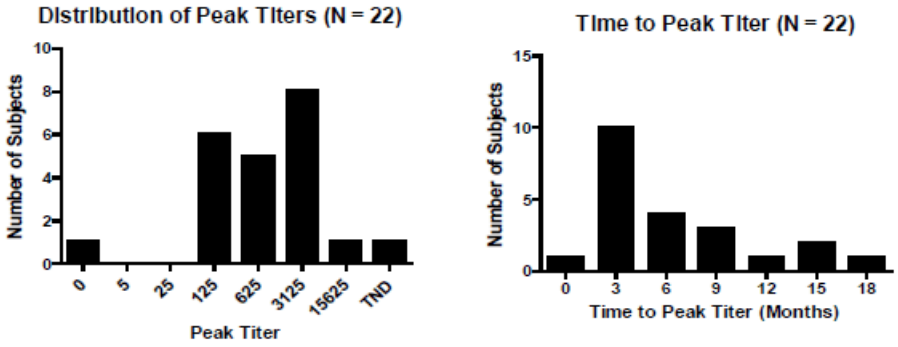
	Obese Subjects (N = 776) Studies 970164, 970213, 980236				Obese Subjects with Type 2 Diabetes (N = 296) Studies 970171 and 970188			
		Metreleptin				Metreleptin		
Preferred Term [2]	Placebo (N = 251) n (%)	10mg [1] (N = 214) n (%)	20mg [1] (N = 374) n (%)	All (N = 588) n (%)	Placebo (N = 100) n (%)	10mg [1] (N = 61) n (%)	20mg [1] (N = 135) n (%)	All (N = 196) n (%)
Any Treatment-Emergent Adverse Event	**207 (82.5)**	**192 (89.7)**	**354 (94.7)**	**546 (92.9)**	**92 (92.0)**	**53 (86.9)**	**125 (92.6)**	**178 (90.8)**
Back pain	14 (5.6)	11 (5.1)	14 (3.7)	25 (4.3)	2 (2.0)	1 (1.6)	3 (2.2)	4 (2.0)
Diarrhoea	11 (4.4)	3 (1.4)	27 (7.2)	30 (5.1)	6 (6.0)	4 (6.6)	8 (5.9)	12 (6.1)
Fatigue	15 (6.0)	8 (3.7)	28 (7.5)	36 (6.1)	9 (9.0)	3 (4.9)	11 (8.1)	14 (7.1)
Headache	33 (13.1)	33 (15.4)	63 (16.8)	96 (16.3)	10 (10.0)	7 (11.5)	20 (14.8)	27 (13.8)
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.0)	9 (14.8)	19 (14.1)	28 (14.3)
Influenza	19 (7.6)	19 (8.9)	22 (5.9)	41 (7.0)	5 (5.0)	1 (1.6)	6 (4.4)	7 (3.6)
Injection site erythema	1 (0.4)	60 (28.0)	25 (6.7)	85 (14.5)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site haemorrhage	15 (6.0)	14 (6.5)	13 (3.5)	27 (4.6)	2 (2.0)	2 (3.3)	2 (1.5)	4 (2.0)
Injection site inflammation	2 (0.8)	27 (12.6)	11 (2.9)	38 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site oedema	0 (0.0)	12 (5.6)	6 (1.6)	18 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pruritus	3 (1.2)	40 (18.7)	19 (5.1)	59 (10.0)	3 (3.0)	1 (1.6)	3 (2.2)	4 (2.0)
Injection site rash	0 (0.0)	11 (5.1)	8 (2.1)	19 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reaction	100 (39.8)	58 (27.1)	272 (72.7)	330 (56.1)	57 (57.0)	41 (67.2)	98 (72.6)	139 (70.9)
Nasopharyngitis	35 (13.9)	36 (16.8)	44 (11.8)	80 (13.6)	9 (9.0)	5 (8.2)	10 (7.4)	15 (7.7)
Nausea	8 (3.2)	10 (4.7)	25 (6.7)	35 (6.0)	9 (9.0)	1 (1.6)	6 (4.4)	7 (3.6)
Oropharyngeal pain	14 (5.6)	5 (2.3)	17 (4.5)	22 (3.7)	2 (2.0)	3 (4.9)	4 (3.0)	7 (3.6)
Sinusitis	12 (4.8)	4 (1.9)	16 (4.3)	20 (3.4)	5 (5.0)	2 (3.3)	8 (5.9)	10 (5.1)
Upper respiratory tract infection	14 (5.6)	1 (0.5)	7 (1.9)	8 (1.4)	12 (12.0)	5 (8.2)	14 (10.4)	19 (9.7)
Urinary tract infection	4 (1.6)	1 (0.5)	3 (0.8)	4 (0.7)	5 (5.0)	1 (1.6)	4 (3.0)	5 (2.6)

QD = once daily; BID = twice daily.
Notes: All 228 subjects in study 970213 received metreleptin during a 4-week induction period. Of these, 189 subjects were subsequently randomized, 126 to metreleptin and 63 to placebo. Hence, data for the 63 subjects randomized to placebo are included in the placebo (randomized treatment period) and metreleptin (induction period) columns as appropriate.
- Treatment-emergent adverse events were defined as any adverse event that began or worsened after subjects received the first dose of randomized study medication; for Study LEPT-970213, they were defined as any adverse event that began or worsened after subjects received the first dose of metreleptin during the 4-week metreleptin induction period for the 228 metreleptin-treated subjects; and any adverse event that began or worsened after subjects received the first dose of placebo during the 24-week treatment period for the 63 subjects randomized to placebo.
- Summaries by individual treatment are based on the treatment at or immediately prior to the onset of the adverse event.
- Subjects experiencing multiple episodes of a given adverse event are counted once in each relevant treatment.
[1] Doses indicated are per day; subjects received 10 mg per day (administered as 10 mg QD) or 20 mg per day (administered as 10 mg BID or 20 mg QD).
[2] Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 10.1 and upversioned to Version 13.0.
Source: ISS, Table 6

7.5.2 Time Dependency for Adverse Events

Time dependency of adverse events could not be formally assessed given the nature of the lipodystrophy data: because the trials are ongoing and since data are presented up to a number of data cuts, the amount of data varies across patients. Nevertheless, limited time-to-peak antibody data are available from a subset of patients from the FHA101 trial (note that some patients only have one post-treatment antibody assessment, and the sampling at intervals of approximately every three months may not be sufficiently frequent to capture the true peak titer).

Figure 33. Peak Titer Distribution and Time to Peak Titer of Antibodies to Metreleptin, FHA101 (N = 22)



7.5.3 Drug-Demographic Interactions

Subgroup analyses by sex and race were not conducted. The majority of patients in the NIH trials and FHA101 were female (83.3% and 92.9%, respectively) and white (61.1% and 75.0%, respectively). While male patients and Black, Asian, Native American, Hispanic, and other races were represented in the patient population, the number of patients was insufficient to examine the effect of either sex or race on adverse events.

See Section 7.6.3, Pediatrics and Assessment of Effects on Growth for a discussion of safety in the pediatric group.

7.5.4 Drug-Disease Interactions

Because lipodystrophy is a heterogenous disorder, certain co-morbidities are more common in certain types of lipodystrophy. For example, renal and liver disease may be more frequently associated with generalized versus partial lipodystrophy. In addition, some serious adverse events seemed to be clustered in the AGL group (e.g., lymphoma, possibly autoimmune diseases). Therefore, an exploratory analysis of adverse events by system organ class was conducted by diagnosis in the NIH trials. Differences between groups may reflect underlying diseases or differences in metreleptin response. Interpretation, however, is limited by the relatively small number of patients per group. Given the proportion of patients in the FHA101 trial with FPL (75%), adverse events presented only by generalized versus partial lipodystrophy are presented.

Table 80. Treatment-Emergent Adverse Events by Lipodystrophy Diagnosis and System Organ Class, NIH Trials

	CGL N=32	CGL%	AGL N=16	AGL%	FPL N=20	FPL%	APL N=4	APL%
Gastrointestinal disorders	12	37.5	4	25.0	7	35.0	3	75.0
Infections and infestations	11	34.4	5	31.3	6	30.0	2	50.0
Musculoskeletal and connective tissue disorders	8	25.0	3	18.8	3	15.0	2	50.0
Metabolism and nutrition disorders	4	12.5	6	37.5	4	20.0	1	25.0
Nervous system disorders	7	21.9	4	25.0	4	20.0	0	0.0
General disorders and administration site conditions	6	18.8	4	25.0	4	20.0	0	0.0
Skin and subcutaneous tissue disorders	5	15.6	2	12.5	6	30.0	1	25.0
Investigations	4	12.5	5	31.3	2	10.0	0	0.0
Renal and urinary disorders	5	15.6	2	12.5	4	20.0	0	0.0
Psychiatric disorders	3	9.4	5	31.3	1	5.0	0	0.0
Reproductive system and breast disorders	5	15.6	1	6.3	2	10.0	0	0.0
Blood and lymphatic system disorders	4	12.5	2	12.5	1	5.0	0	0.0
Respiratory, thoracic and mediastinal disorders	4	12.5	1	6.3	2	10.0	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	9.4	2	12.5	1	5.0	0	0.0
Vascular disorders	3	9.4	3	18.8	0	0.0	0	0.0
Cardiac disorders	2	6.3	2	12.5	0	0.0	0	0.0
Endocrine disorders	2	6.3	0	0.0	2	10.0	0	0.0
Eye disorders	0	0.0	1	6.3	3	15.0	0	0.0
Hepatobiliary disorders	0	0.0	3	18.8	1	5.0	0	0.0
Injury, poisoning and procedural complications	1	3.1	1	6.3	0	0.0	0	0.0
Immune system disorders	0	0.0	0	0.0	1	5.0	0	0.0
Surgical and medical procedures	0	0.0	0	0.0	1	5.0	0	0.0

Source: Reviewer generated from BLA 125390 datasets

Table 81. Treatment-Emergent Adverse Events by Generalized vs. Partial Lipodystrophy and System Organ Class, FHA101

	Generalized Lipodystrophy (N = 5)		Partial Lipodystrophy (N = 23)		All Patients (N = 28)	
System Organ Class	n (%) Events	EAER	n (%) Events	EAER	n (%) Events	EAER
All Adverse Events	**5 (100.0) 37**	**6.58**	**22 (95.7) 148**	**5.09**	**27 (96.4) 185**	**5.33**
Blood and lymphatic system disorders	1 (20.0) 1	0.18	3 (13.0) 5	0.17	4 (14.3) 6	0.17
Gastrointestinal disorders	4 (80.0) 14	2.49	12 (52.2) 25	0.86	16 (57.1) 39	1.12
General disorders and administration site conditions	2 (40.0) 2	0.36	11 (47.8) 18	0.62	13 (46.4) 20	0.58
Injury, poisoning and procedural complications	0 (0.0) 0	0.00	4 (17.4) 5	0.17	4 (14.3) 5	0.14
Metabolism and nutrition disorders	1 (20.0) 1	0.18	8 (34.8) 14	0.48	9 (32.1) 15	0.43
Musculoskeletal and connective tissue disorders	0 (0.0) 0	0.00	8 (34.8) 13	0.45	8 (28.6) 13	0.37
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (20.0) 1	0.18	0 (0.0) 0	0.00	1 (3.6) 1	0.03
Renal and urinary disorders	1 (20.0) 1	0.18	2 (8.7) 3	0.10	3 (10.7) 4	0.12
Reproductive system and breast disorders	1 (20.0) 1	0.18	2 (8.7) 2	0.07	3 (10.7) 3	0.09
Respiratory, thoracic and mediastinal disorders	1 (20.0) 1	0.18	3 (13.0) 3	0.10	4 (14.3) 4	0.12
Skin and subcutaneous tissue disorders	2 (40.0) 6	1.07	2 (8.7) 2	0.07	4 (14.3) 8	0.23

EAER = Exposure Adjusted Event Rate, calculated as dividing number of events by patient years of exposure as of data cutoff.
Notes: Treatment-emergent adverse events are defined as those that occurred during or after the first injection of metreleptin through the remainder of the study.
- n (%), where n represents number of patients experiencing at least one occurrence of a given event, %=100*n/N.

Source: Clinical Safety Update, Table 51

Adverse events were presented in the Amgen obesity five-study ISS by whether or not patients had a diagnosis of type 2 diabetes (since three trials evaluated a population of obese patients without type 2 diabetes and two trials were conducted in patients with obesity and type 2 diabetes). The only commonly-occurring adverse event identified that occurred in diabetes-only patients (and to a greater extent in metreleptin- versus placebo-treated patients), was hypoglycemia (see Section 7.3.5, Submission Specific Safety Concerns).

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction evaluations were conducted in the lipodystrophy population. The only interaction that was decribed in this population was a pharmacodynamic interaction (hypoglycemia) between metreleptin and anti-hyperglycemic medications.

In the NIH trials, hypoglycemia was reported in eight (11.1%) of 72 patients, and occurred only in patients also using insulin (with or without oral anti-hyperglycemic agents). The investigator felt that most hypoglycemia events were related to concomitant insulin and metreleptin use, likely resulting from inadequate reductions in insulin doses in the face of marked improvements in insulin sensitivity associated with metreleptin treatment. In FHA101, hypoglycemia was reported in seven (25.0%) of 28 patients. All patients who experienced hypoglycemia adverse events were receiving either concomitant insulin therapy or a sulfonylurea, with or without other oral anti-hyperglycemic agents, except for one patient who was on insulin until about 3 to 4

months before the event of hypoglycemia but was only on metformin at the time of the event.

Reviewer comment: While it is most likely that patients who develop hypoglycemia on metreleptin will be taking other anti-hyperglycemic medications, note that in the Amgen ISS, adverse events described by the preferred term 'hypoglycemic reaction' not only occurred in patients who were on anti-hyperglycemic medications, but also in patients with diabetes who were controlled with diet only (13% metreleptin, 6% placebo in the diet-only diabetes trial).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Background

Metreleptin is not genotoxic and no adverse hematological effects or bone marrow abnormalities were observed in the chronic mouse and dog toxicity studies.[40] The Division is aware, however, of an extensive literature that suggests a link between leptin and cancer (reviewed in 41, 42).

Upon learning of the third case of non-Hodgkin's lymphoma (NHL) in the lipodystrophy program in early 2013 (narratives are presented later in this section), our Division consulted experts from FDA's Division of Hematology Products (DHP) to evaluate these cases. Because hematological malignancies have been reported in the literature in patients with lipodystrophy not treated with metreleptin (see the table below; note that the cutaneous manifestations of the two cases of T-cell lymphomas presented concurrently with fat atrophy), we additionally asked about the expected prevalence of NHL in a population this size (N = 125, including data from the four-month safety update) and whether certain types of lipodystrophy could render a patient more susceptible to hematological malignancy.

Table 82. Reports of Hematological Malignancies in Patients Diagnosed With Lipodystrophy Who Were Not Being Treated With Leptin

Patient	Malignancy	Summary
Male / AGL	Peripheral T-cell lymphoma	Male patient with Down syndrome who developed cutaneous peripheral T-cell lymphoma with AGL[43]
Male / lipoatrophy and panniculitis	Peripheral T-cell lymphoma presenting as lipoatrophy	47-year-old man with lymphoma presenting as panniculitis developing into profound lipoatrophy[44]
Female / partial lipodystrophy and scleroderma	Hodgkin's lymphoma	22-year-old female with generalized lipodystrophy and scleroderma who developed Hodgkin's lymphoma. The authors note that Sjögren's syndrome has been associated with lipodystrophy, scleroderma, and malignant lymphoma and suggest the possibility that lipodystrophy and scleroderma may contribute to the development of Hodgkin's disease or malignant lymphoma.[45]
Female / partial lipodystrophy	Pre-B ALL	Patient with partial lipodystrophy, acanthosis nigricans, and insulin resistance who developed pre-B ALL[46]

Source: BMS Metreleptin PubMed Literature Search; submission 24 Jun 2013; Table 6

The median age at diagnosis for NHL is 66 years, and the incidence of NHL increases with increasing age. The incidence in males is 23.8 per 100,000 and the incidence in females is 16.3 per 100,000.[47] The incidence for NHL in patients with lipodystrophy treated with metreleptin in the BLA trials is 1 of 17 enrolled male patients or 5.9% and 2 of 108 female patients or 1.9%, which translates to 5900 per 100,000 in males (a 248-fold increase over the incidence in the general population) and 1900 per 100,000 in females (a 117-fold increase). In addition, all three NIH patients developed T-cell lymphoma, which is much rarer. The incidence of T-cell lymphoma in the U.S. for males is 2.3 per 100,000 and for females is 1.4 per 100,000;[47] the incidence of T-cell lymphoma in the trials is a 2565-fold increase and a 1357-fold increase for males and females, respectively. Note that because of the small population in the BLA clinical trials (N = 125, including the patients in the four-month safety update), these estimates have wide confidence intervals.

Whether the increased risk of NHL (or, more specifically, T-cell lymphoma) is related to the underlying condition (lipodystrophy) or the treatment (metreleptin) is unknown.

Immunodeficiency and autoimmunity are associated with an increased risk for NHL.[48,49,50,51] Despite the few isolated case reports of concurrent diagnoses of lipodystrophy and lymphoma (see table above), a case series of patients with lipodystrophy without metreleptin treatment to adequately evaluate the risk of development of lymphoma in patients with non-HIV lipodystrophy is not available. Furthermore, it is biologically plausible that metreleptin could impact susceptibility to NHL and other malignancies, as described below:§§§§§§§§§§

Leptin is a cytokine that uses the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway for signal induction. Leptin binding activates JAKs, which in turn phosphorylates cytokine receptors which allows selective binding of the STAT family.[52,53] Dysregulation of STAT proteins contributes to the pathogenesis of various types of lymphoid malignancies. Increased activity of STAT3 was reported in T-cell large granular lymphocytic leukemia.[54,55] Constitutive activation of STAT3 and STAT5 has also found to be an important event in the pathogenesis of anaplastic large cell lymphoma, T-cell angioimmunoblastic lymphoma, and Sezary syndrome.[52,56] Leptin exerts proliferative and antiapoptotic activities in a variety of cell types, including T lymphocytes, leukemia cells, and hematopoietic progenitors.[57] Leptin also affects cytokine production, the activation of monocytes/macrophages, wound healing, angiogenesis, and hematopoiesis. *In vivo*, leptin regulates inflammation, playing an inhibitory role on monocyte/ macrophage-mediated responses while exerting a permissive role on lymphocyte-mediated inflammation. Leptin either induces or increases cell proliferation of different cell types, including T lymphocytes, CD34+ cells, leukemia cells, and endothelial cells. Leptin also acts as an inhibitor of glucocorticoid-induced apoptosis in T lymphocytes and of apoptosis induced by cytokine withdrawal in leukemia cells.[58]

In addition to the specific question of lymphoma, the Division requested the sponsor conduct a literature search of leptin and cancer in general. The effects of leptin on cancer cell growth in *in vitro* and non-clinical studies are summarized in the following table:

§§§§§§§§§§ Background provided by DHP Reviewer, Karen McGinn

Table 83. Effects of Leptin on Cancer Cell Growth Based on In Vitro and Non-Clinical Studies

Cancer Type	Effect on Cell Growth
Breast	• ↑ cell proliferation[59,60,61,62,63,64,65] • ↑ anchorage-independent growth[60] • ↑ ERK1/2, STAT3, Akt/GSK3, and PKCα pathways[59,60,61,62,63,64,65] • ↑AP1→↑cdk2, cyclinD1, pRb[60,62,64] • ↑AP1→↑aromatase[63] • →cMyc[65] • Modulates ER signaling[64] • ↑HER2 via EGFR and JAK[66,67] • Levels correlate with hTERT and BMI[68]
Colorectal	• ↑ cell invasion via PI3K→Rac and RhoA[69] • ↑cell growth via ↑ERK1/2[70,71] • PPAR-γ ligands ↑ ERK1/2 and compete[72,73,74] • NFκB→↓apoptosis[75]
Prostate	• ↑cell proliferation[76] • ↓apoptosis • ↑ERK1/2 in hormone resistance (HR)[77] • ↓cell growth in HR antagonized by insulin[78] • ↑JAK2/STAT3, p38 MAPK, and PKC→↑apoptosis[79] • In HR cells, ↑ AR →↓ apoptosis • ↑αvβ3 integrin via OBR1/IRS-1/PI3K/Akt/NF-κB →↓migration[80] • High leptin levels →↓proliferation & angiogenesis[81] • Leptin dose-dependent ↓ HR cell migration & invasion[82] • ↑proliferation via MAPK and PI3-K[77] • Leptin:adiponectin ratio affects proliferation via p53 and BCL-2[83]
Pancreatic	• ↓cell proliferation[84] • ↑STAT3 and STAT5b pathways[85] • ↓leptin & ↑adiponectin/leptin ratio in PC cells[86] • ↑MT1-MMP via KIF1B →↑ invasion[87] • Suppress SOCS3 →↑ leptin & STAT2 →↑ tumor development[88] • ↑JAK/STAT3 and STAT5b pathways[89,85]
Gastric	• ↑EGFR and JAK[90] • ↑STAT3 signal via OBR[88] • Time & dose-dependent ↓ proliferation via G0/G1 arrest[91] • ↑apoptosis via caspases 3 and 8[91]
Ovarian	• ↑ERK1/2 →↑cell proliferation[92] • Time- and dose-dependent ↑proliferation via ↓forkhead box O3 and p27, Bim[93] • ↑MEK/ERK1/2 and PI3K/Akt →↑cyclin D1, MCL-1 →↑proliferation and ↓ apoptosis[94,92] • ↑S and G2/M phases via ↑cyclins D & A, and ↓p21WAF1/CIP1 →↑proliferation[95] • ↓Bad, TNFR1, and caspase 6 →↓apoptosis[96] • ↑ERα signal via STAT3 →↑ proliferation
Lung	• ↑ERK1/2 →↑cell proliferation[97]
Leukemia and lymphoma	• LepRb and OBR mRNA detected in myeloid and leukemic lymphoid cell lines[98] • ↑cell proliferation in human myeloid leukemia cell lines and cell isolates from patients[99] • Additive or synergistic growth effects when combined with hematopoietic cytokines (e.g., IL-3, G-CSF, and SCF)[100] • ↑Bcl-2, cyclin D1 →↑cell cycle entry[101] • ↓ apoptosis → overall B-cell homeostasis

	• ↑PI3K/AKT → ↑ proliferation and ↓ apoptosis in DLBCL[102]
Thyroid	• ↑OBR expression in 80% of PTC tumors[103,104] • ↑XIAP (antiapoptotic protein) and PI3K/Akt → ↓ apoptosis & ↑ proliferation • ↑cell growth[105] • ↓ apoptosis • Modulates migration of cancer cells; ↓ follicular & anaplastic migration[106] • ↑MEK/ERK1/2 and PI3K/Akt →↑papillary migration
Hepatic	• Controversial role; promote HCC development or tumor growth inhibition[107,108] • Promotes fibrosis, angiogenesis • ↑TGFβ, type-I procollagen and tissue inhibitor of metallo-proteinase-1 via OBR[109,110] • ↑VEGF via HIF1a[110] • Leptin associated with NAFLD and NASH, which contribute to fibrosis and HCC[111] • In leptin deficiency, ↑NF-κB/p65, proinflammatory cytokines, proliferating cell nuclear antigen, and cell survival signals[112]
Skin/Melanoma	• ↑NO and circulating EPCs →↑vasculogenesis[113]

Abbreviations: Akt, Protein kinase B; AP1, activator protein 1; AR, androgen receptor; Bad, Bcl-2-associated death promoter; BCL-2, B-cell lymphoma 2; BMI- body mass index; cdk, Cyclin -dependent kinase; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; EPC, endothelial progenitor cell; ER, estrogen receptor; ERK, extracellular signal regulated kinases; G-CSF, Granulocyte colony-stimulating factor; GSK, Glycogen Synthase Kinase; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HIF1a, hypoxia inducible factor 1; HR, Hormone resistant; hTERT, human telomerase reverse transcriptase; IL-3, interleukin 3; IRS, Insulin receptor substrate; JAK, Janus kinase; KIF1B, kinesin family member 1B; MAPK, mitogen-activated protein kinases; MCL, Induced myeloid leukemia cell differentiation; MEK, mitogen-activated protein kinase (MAPK) kinase; MT1-MMP, Matrix metalloproteinase; NAFLD, nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; NFκB, Nuclear Factor-Kappa B; OBR1, long form of the leptin receptor; NO, nitric oxide; OBR, leptin receptor; p21WAF1/CIP1, cyclin-dependent kinase inhibitor 1; PC, prostate cancer; PI3K, Phosphoinositide 3-kinase; PKC, Protein kinase C; PPAR, peroxisome proliferator-activated receptors; pRb, phosphorylated retinoblastoma protein; PTC, papillary thyroid cancer; Rho, Ras homolog; SCF, Skp, Cullin, F-box containing complex; SOCS3, suppressor of cytokine signaling 3; STAT, Signal Transducer and Activator of Transcription; TGF, Transforming growth factor; TNFR1, TNF receptor 1; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein

Source: BMS Metreleptin PubMed Literature Search; submission 24 Jun 2013; Table 4

Reviewer comment: While there are some conflicting data from the* in vitro *studies, on balance it appears that leptin signaling promotes cell growth and survival and inhibition of apoptosis. These findings support plausible mechanisms whereby metreleptin may promote tumor growth in a susceptible patient.

Observational data suggest that elevated leptin concentrations and leptin/leptin receptor tissue expression may be associated with certain cancers in humans. The long form leptin receptor (Ob-Rb) is present in hypothalamic regions implicated in the regulation of feeding behavior and energy balance, whereas the short leptin receptor isoforms are expressed in choroid plexus, vascular endothelium, and peripheral tissues, such as kidney, liver, lung, and gonads.[5] High leptin receptor expression has been found in pancreatic insulinoma,[41] and also in tumors and sera of patients with endometrial cancer,[114] thyroid cancer,[115] and in some studies of leukemia/lymphoma.[116]

Leptin serum concentration was associated in some,[64,117] but not all,[118] publications of breast cancer, colorectal cancer (men only),[64] and one study of chronic lymphocytic leukemia with increased risk factors for cancer;[116] leptin concentrations were higher with

advanced cancer stage in some but not all studies. Leptin tissue expression was present in some reports of prostate cancer,[64] endometrial cancer, [119] and thyroid cancer.[115]

Cancer in the Metreleptin Clinical Trials

The sponsor summarized the individual patient data for malignancies in patients treated in metreleptin clinical trials and compassionate use programs; the summary table is below and discussion of individual cases follows. In summary, there were:

- Hematological malignancies: three cases of T-cell lymphoma, all in patients with AGL, and one case of lymphocytic leukemia in a patient with obesity (case described in Section 7.3.1, Deaths)

- Papillary thyroid cancer: one case in patient with CGL, and two********** cases in patients with obesity

- Breast cancer: One case in a patient with FPL, one case (*in situ*) not reported in the table below in a patient with AGL (see patient 90147, T-cell lymphoma), and two cases in patients with obesity
    - In addition, one case of breast cancer was reported in a patient with obesity treated with placebo

- Skin cancer: Two cases of malignant melanoma and two cases of basal cell carcinoma, all in patients with obesity, and one case of squamous cell carcinoma of the tongue in a patient with lipodystrophy associated with HIV.
    - In addition, two cases of basal cell carcinoma were reported in patients with obesity treated with placebo

- Others: One case of metastatic adenocarcinoma (AGL), one case of bile duct cancer (lipodystrophy patient in Japan), and one case of vaginal carcinoma in a patient treated with Fc-leptin (Amgen program)
    - In addition, one case of cervix carcinoma and one case of lung cancer were reported in patients treated with placebo

********** There was a fourth case of a patient treated with 12 doses of metreleptin who was diagnosed with papillary thyroid cancer one year after study discontinuation. This case was included in the table below, but given the short treatment duration and long duration off metreleptin, was not included in my count.

Table 84. Individual Patient Data for Malignancies

Cases Involving Administration of Metreleptin

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
LD	BLA, Clinical Safety Update	T-cell lymphoma	T-cell cutaneous lymphoma	68 yr, M	Acquired generalized LD hypercellular marrow, leucopenia, pancytopenia, anemia, lymphadenopathy, enlarged spleen, hepatic cysts, hepatomegaly	249	Fatal (~6 months after discontinuing metreleptin treatment)	Skin nodule was noted and skin biopsy result compatible with peripheral T-cell lymphoma.
LD	BLA, Clinical Safety Update	T-cell lymphoma	T-cell lymphoma	59 yr, F	Acquired generalized LD (1999), severe intermittent neutropenia (Dec 2007), benign breast fibroma, lipoatrophic diabetes, non alcoholic steatohepatitis, goiter (multinodular), thyroidectomy, hepatosplenomegaly	210-240	Fatal (~7 months after discontinuing metreleptin treatment)	Neutropenia returned Jan-2008. Bone marrow biopsy revealed hypercellular bone marrow with marked atypical T-cell lymphocytosis and myeloid maturation with left shift. On an unspecified date subject developed skin nodules. Skin biopsy performed Jan-2009 revealed subcutaneous T-cell lymphoma, stage IV-A. Chemotherapy initiated.
LD	BLA, Clinical Safety Update	T-cell lymphoma	Anaplastic large cell lymphoma	13 yr, F	Acquired generalized LD, hyperinsulinism, severe insulin resistance, nonalcoholic steatohepatitis, hypertriglyceridemia, hypertension, advanced bone age	661	Not Resolved	Subject noted bump under Right breast (Dec2012). Ultrasound consistent with enlarged lymph node. Biopsy of mass performed and pathology results showed "anaplastic large cell lymphoma, ALK positive'. Leptin therapy was stopped on 25Dec12 and reinitiated on 12Feb13.
Obesity	BLA, Amgen 5-study ISS and in Clinical Safety Update discussion	Lymphocytic leukemia	Lymphocytic leukemia	67 yr, F	Obesity	28	Fatal	Patient was hospitalized with pneumonia 28 days after initiate study drug, lab test showed neutrophils 2%, lymphocytes 95%. A diagnosis of lymphocytic leukemia was made, treated with IV antibiotics and chemotherapy. Patient expired 2 months later.

Cases Involving Administration of Metreleptin (continued)

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
LD	BLA, Clinical Safaety Update	Papillary thyroid cancer	Metastatic Papillary Thyroid Carcinoma	24 yr, F	Congenital generalized LD, Hashimoto's thyroiditis, lipoatrophic diabetes, insulin resistance Hypertriglyceridemia, pancreatitis	705	Recovered/Resolved (thyroidectomy)	Diagnosed with multiple thyroid nodules summer 2009; Pathology (APR2011): Metastatic papillary thyroid carcinoma involving 1 lymph node; multifocal papillary cancer, involving right isthums/pyramidal & left lobes; Hashimoto's chronic thyroiditis.
Obesity	BLA, DFA102 CSR, and assessment provided to FDA on 17 January 2011	Papillary thyroid carcinoma	Papillary thyroid carcinoma	51 yr, F	Obesity, thyroid mass, Seasonal allergic rhinitis, drug allergy (Sulfa drugs)	45	Resolved (thyroidectomy)	Thyroid mass diagnosed in Jul 2008, prior to initiation of study drug. Histopathology revealed papillary thyroid carcinoma.
Obesity	BLA, DFA102 CSR, and assessment provided to FDA on 17 January 2011	Papillary thyroid carcinoma	Papillary thyroid carcinoma	61 yr, F	Obesity, Enlarged thyroid (1981), a family of thyroid cancer (2 sisters)	166	Resolved (thyroidectomy)	Thyroid pathology report (Jun2009): Papillary carcinoma (1.0) limited to thyroid. Nodular hyperplasia and chronic thyroiditis. No lymphatic /capillary invasion or extrathyroid extension was noted
Obesity	Reported via investigator IND and included in the submission	Thyroid cancer	Thyroid cancer	22 yr, F	Obesity, thyroglossal duct cyst	515	Not Resolved	Approximately 1 year post completion of study, diagnosed with papillary thyroid cancer. No additional information. PK study with only ~12 doses administered over several weeks
Obesity	In DFA103 study CSR, submitted 20 June 2013	Invasive ductal breast carcinoma	Invasive ductal carcinoma, right breast	58 yr, F,	Obesity, pre-existing skin bump at the right axillary area (05/2010)	17	Unknown	Pre-existing skin bump at the right axillary area (05/2010), diagnosed as 'inflamed sweat gland'). Pathology report (10Feb2011) revealed that right axillary lymph node was positive for invasive mammary carcinoma

Cases Involving Administration of Metreleptin (continued)

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
LD	Reported via investigator IND and included in the submission	Breast cancer	Breast cancer	50 yr, F	Familial partial liposystrophy, hypertriglyceridemia, hepatic steatosis, myocardial infarction.	2903	Not reported	Diagnosed with stage 1 breast cancer after suspicious mammogram led to needle biopsy (29Apr2013). Outpatient mastectomy performed on 13May2013. Self reported by the patient, no medical records obtained yet.
Obesity	In BLA, Amgen 5-ISS	Breast cancer	Inflamed breast cancer (malignant)	51 yr, F	Obesity, Removal of benign lipoma Right breast (1980); hysterectomy (1987); hormone replacement treatment (since 1996, estrogen patch), hypothyroidism	324	Not reported	Patient had right breast discomfort in 1999; Biopsy right breast (19May1999) revealed inflammatory carcinoma of the skin and infiltrating ductal carcinoma. 05Aug1999 mammogram review of films from 1993-1995; 1995 films showed increased density in the area of the breast; subsequently diagnosed breast cancer. Investigator reported in summary: "It is possible that the film of 1995, which was taken before study, represents an abnormality that may have progressed to breast cancer."
Obesity	BLA, DFA102E CSR,	Malignant melanoma	Melanoma L Shoulder	51 yr, F	Obesity	100	Resolved	Non serious event noted on CRF. No further information.
Obesity	BLA, 5-study, Amgen 5-ISS	Malignant melanoma	5-6 cm firm lymph node 1 axilla (malignant melanoma)	68 yr, M	Lip and/or oral cavity cancer (1993); chest melanoma (1997), both surgically removed. Obesity, diabetes, hypertriglyceridemia, smoker (11 years)	150	Not reported	On 21Nov1998 physical exam found 5-6 CM firm lymph node on left axilla; biopsy performed (05Jan1999) revealed malignant melanoma; MRI revealed a 2-3 cm lesion in the left temporal lobe later with diagnosis 'brain metastasis with edema'.
Obesity	BLA, 5-study, Amgen 5-ISS	Basal cell carcinoma	Base cell cancer on (R) ear and nose	68 yr, M	Hodgkin's lymphoma (1957), smoker (12 years), hypercholesterolemia	480	Resolved (surgical removal of lesion)	Skin lesions on ear and nose were found during clinical study visit. Biopsy of right side of nose where glasses rest revealed basal cell carcinoma
Obesity	BLA, DFA102 CSR	Basal cell carcinoma	Basal cell carcinoma on face	57 yr, F	Obesity, hypercholesterolemia, allergy	129	Resolved	Non serious event noted on CRF, no further information.

Cases Involving Administration of Metreleptin (continued)

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
LD	BLA, Clinical Safety Update	Worsening of metastatic adenocarcinoma	adenocarcinoma, worsening	67 yr, F	AGL, known history of metastatic adenocarcinoma	78	Fatal	Subject had progressive adenocarcinoma of undetermined origin, complicated by a small bowel obstruction and apparent sepsis
HIV- related LD	Reported via investigator IND and included in the submission	Squamous cell carcinoma of the tongue	Squamous cell carcinoma of the tongue	49 yr, M	LD, hypertriglyceridemia, AIDS, Tongue lesion present prior to study initiation. 20 pack a year history of smoking.	64	Unknown	Developed tongue lesion after tongue cut on jagged crown, increasing in size in May 2006 prior to initiating Leptin vs. placebo. Biopsy of epiglottis (1988); no results. Pathology (date unknown) left lateral tongue lesion revealed squamous cell carcinoma.
LD	Reported in JNDA (KUTR-003-0)	Bile duct cancer	Hepatic mass	35 yr, F	Hypertension, hypertriglyceridaemia, hyperuricaemia, hepatic steatosis, diabetes mellitus diabetic neuropathy, diabetic retinopathy, pancytopenia,asteatotic leg dermatitis, amenorrhoea	791	Fatal	Sponsor requesting additional detail.

Cases Involving Administration of FC-leptin

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
Obesity	Included in this submission as part of the Amgen studies outside the Amgen 5-study ISS	Vaginal cancer	Vaginal cancer	36 yr, F	History of abnormal pap smear (Sep 1999) with repeat also abnormal (Apr 2000). obesity	20	Not Resolved	Culposcopy 12May2000 initially inconclusive, final result (31May2000) revealed vaginal cancer. Subject withdrew from study on 26May2000 to undergo radiation treatment. No additional information.

Cases Involving Administration of Placebo								
Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
Obesity	BLA, Amgen 5-study ISS	Cervix carcinoma	Cervix carcinoma	48 yr, F	Abnormal pap smear 22Dec1998, on birth control pills, Obesity	81	Unknown	Repeat pap smear (22-Mar-1999) abnormal; cervical biopsy (27-Mar-1999) revealed adenocarcinoma in situ; subject early termed from study due to family emergency.
Obesity	BLA, DFA104 CSR	Lung adenocarcinoma	Lymphangitic adenocarcinoma of the lung	60 yr, F	Obesity, persistent cough (Dec2010)	36	Fatal	Patient had history of persistent cough since Dec2010, prior to study enrollment. Apr-2011: Pathology from bronchoscopy: Adenocarcinoma of right lung bronchial washings. Pleural fluid positive for malignancy.
Obesity	BLA, DFA102 CSR	Basal cell carcinoma	Basal cell carcinoma on tip of nose	40 yr, F	Obesity	164	Resolved	Non serious event reported on CRF, no further information.
Obesity	BLA, DFA104 CSR	Basal cell carcinoma	left shoulder basal cell carcinoma	20 yr, F	Obesity	36	Resolved	Non serious event reported on CRF, no further information.
Obesity	BLA, Amgen, 5-study ISS	Breast cancer stage III	Adenocarcinoma - stage 3 - right breast	49 yr, F	Obesity, Lymphedema, On estrogen since 1995, obesity	300	Unknown	Fine needle and core biopsy on 21-Jan-2000 revealed Stage 3 adenocarcinoma. Early termination (study ended early) on 30-Dec-1999.

Source: Response to FDA Request for Information Dated 24-May-2013 (question 3); submission 24 Jun 2013; Table 3-14 (revised)

Patients with Lipodystrophy

There were seven known events of cancer, including three cases of T-cell lymphoma, in the NIH and FHA101 trials. Further details are presented below.

- T-cell cutaneous lymphoma: At study entry, patient 90115 (NIH Trial) was a 68-year-old man with AGL, as well as severe insulin resistance, diabetes mellitus, hypertriglyceridemia, abnormal liver function tests, and hepatosplenomegaly. In July 1997, five years prior to starting metreleptin (May 2002), he was evaluated for leukopenia (WBC 2000/µL) with relative neutropenia and was diagnosed with chronic idiopathic neutropenia. A lymph node biopsy and bone marrow biopsy in 1998 were non-diagnostic. Erythropoeitin was prescribed started in 2001. In early May 2002, another bone marrow biopsy showed a markedly hypercellular marrow with erythroid predominance and reactive lymphoid nodules. Peripheral blood smear showed moderate leukopenia, mild normochromic, normocytic anemia, and mild thrombocytopenia. In mid May 2002, the patient was evaluated at the NIH for generalized lipodystrophy and started on metreleptin treatment, while still taking erythropoietin. At the time of initial evaluation, he was noted to have diffuse lymphadenopathy on exam as well as 1-2 small skin lesions on his leg that did not appear concerning on a background of sun-damaged skin. He received a trial of G-CSF of unspecified duration from his local hematologist for leukopenia. At a four-month follow-up visit at the NIH, a liver biopsy showed no specific features of steatohepatitis, and abdominal ultrasound showed splenomegaly. He continued to have lymphadenopathy on exam. At his eight-month follow-up visit, repeat abdominal ultrasound showed no change in the splenomegaly. Over the preceding month, the patient had noted progression of the skin lesions on his leg with increased size and number of the lesions. Skin biopsy revealed peripheral T-cell

lymphoma. Metreleptin treatment was discontinued at that time. Bone marrow biopsy performed the next month showed hypercellular bone marrow with trilineage hematopoiesis, erythroid hyperplasia, and atypical lymphoid infiltrate suggestive of involvement by peripheral T-cell lymphoma. On peripheral blood, clonal rearrangement of the T-cell receptor gamma chain was detected. Based on the fact that the skin lesions were present at baseline prior to initiation of metreleptin treatment, and given that the progression could be consistent with the natural history of the condition, the peripheral T-cell lymphoma was not reported as an adverse event at that time.

Reviewer comment: The correlation between metreleptin and the development of T-cell lymphoma is confounded by signs of myelosuppression at baseline, the use of another cytokine (G-CSF), and abnormal bone marrow biopsies prior to initiation of metreleptin therapy. In addition, the patient was taking erythropoietin, and had lymphadenopathy, hepatosplenomegaly, and skin lesions before starting metreleptin.

- T-cell lymphoma / breast cancer: At study entry, patient 90147 (NIH Trial) was a 59-year-old female from Spain who was first seen at the NIH in May 2008 for evaluation and treatment of AGL that had developed over the past 10 years. She had a recent history of neutropenia diagnosed in Dec 2007 for which she was briefly treated with G-CSF (Neupogen) with normalization of her neutrophil count. However, the neutropenia recurred in Jan 2008, and the G-CSF was restarted. On 11 Jan 2008, a bone marrow biopsy revealed hypercellular bone marrow with marked atypical T-cell lymphocytosis and myeloid maturation with left shift. At her baseline visit at the NIH in 2 Jun 2008, her WBC was normal at 7240/µL with a normal neutrophil count of 2150/µL, and elevated lymphocyte count of 4200/µL (on G-CSF treatment). She was started on metreleptin on 04 Jun 2008, and returned home to Spain to continue metreleptin treatment. This was her only visit to the NIH. The patient had a history of a benign breast fibroma. In Oct 2008, she was diagnosed with intraductal breast carcinoma. In (b) (6), she underwent a right complete mastectomy. Lymph nodes (43) were clear. She was treated with tamoxifen. On an unspecified date, the patient's husband reported that she experienced sores in her throat, a persistent cough, and after approximately 10 days, developed blurry vision. She was diagnosed with cataracts. The patient then developed skin nodules and corneal ulcers. A skin biopsy performed in Jan 2009 revealed cutaneous T-cell lymphoma, stage IV-A. On an unspecified date in Feb 2009, CD4+ T-cell lymphoma infiltration was seen in cerebrospinal fluid; data suggested an "SP infiltration" (not defined further) through clonal lymphoid T-cells. A CT scan performed on 20 Feb 2009 showed hepatosplenomegaly, with a small cystic lesion in the right hepatic lobe (both similar to previous imaging studies performed on 22 Jan 2009). It did not show significant changes in terms of lymphoma staging. The patient was instructed to stop metreleptin by the investigator after tapering down for one week. The last dose of metreleptin was taken on 31 Jan 2009. Chemotherapy treatment was initiated on

19 Feb 2009 utilizing fludarabin, cyclosphosphamide, and doxorubicin. Tamoxifen was suspended while undergoing chemotherapy treatment. She was discharged on an unspecified date with a hemoglobin of 8.0 g/dL (normal range: 12.0-16.0 g/dL), platelet count of 99.0 x 1000/µL (normal range: 150.0-425.0 x 1000/µL), elevated peripheral leukocyte count of 17.4 x 1000/µL (normal range: 4.0-11.0 x 1000/µL) and peripheral neutrophils 14.5 x 1000/µL (normal range: 1.9-8.0 x 1000/µL). Her peripheral lymphocyte count was normal at 2.2 x 1000/µL (normal range: 0.9-5.2 x 1000/µL). She was scheduled to start her third cycle of chemotherapy on 04 Mar 2009. Based on subsequent information from the investigator, the patient died on (b) (6) (b) (6). According to the patient's husband, the cause of death was "multi system organ failure related to the lymphoma." According to the investigator, "leptin did not cause the lymphoma but may potentiate the paraneoplastic tendencies inherent in the underlying disease of the patient."

Reviewer comment: The correlation between metreleptin and the development of T-cell lymphoma is confounded by signs of myelosuppression at baseline, the use of another cytokine (G-CSF), and abnormal bone marrow biopsies prior to initiation of metreleptin therapy.

- Metastatic papillary thyroid carcinoma: At study entry, patient 90156 (NIH Trial) was a 22-year-old Hispanic female patient with CGL and a relevant past medical history of Hashimoto's thyroiditis of unknown duration. The patient was diagnosed with multiple thyroid nodules in the summer of 2009 (month unknown), approximately a few months after starting metreleptin. In Nov 2010, during a visit to the NIH clinical study site, an ultrasound of the thyroid showed seven nodules (two left, two right, three isthmus). Fine needle aspiration showed some nodules to have atypia of undetermined significance (suspicious of thyroid cancer). On (b) (6), after approximately 1.9 years of treatment with metreleptin, the patient was admitted to the NIH for a total thyroidectomy. Pathology results showed metastatic papillary thyroid carcinoma involving one lymph node, multifocal papillary cancer involving the right isthmus/pyramidal and left lobes, and Hashimoto's chronic thyroiditis. The patient was discharged on (b) (6) without complications. According to documentation provided in the four-month safety update, the patient received definitive treatment with I-131 radioablation on 9 Jan 2012.

- Progressive adenocarcinoma: The narrative for this event was presented in Section 7.3.1, Deaths.

- Anaplastic large cell lymphoma: At study entry, patient 90170 (NIH Trial) was an 11-year-old female with AGL. Relevant medical history included hypertension, hypertriglyceridemia, hyperlipidemia, severe insulin resistance, and non-alcoholic steatohepatitis with possible cirrhosis. Her only medication was metformin 750 mg BID for severe insulin resistance. She had no known autoimmune disease or hematologic abnormalities, and there was no family history of malignancy or

autoimmune diseases. A comprehensive work-up for autoimmune markers (including antinuclear Ab, anti-ENA, thyroid peroxidase Ab, anti-thyroglobulin Ab, GAD65 Ab, anti-cardiolipin Ab, antimitochondrial Ab, anti-neutrophil cytoplasmic Ab, rheumatoid factor) was negative, and complement and quantitative immunoglobulin levels were normal. Baseline labs included HbA1c 5.3%, FPG 108 mg/dL, insulin 251 uIU/mL, TG 368 mg/dL, ALT 36 U/L, AST 20 U/L, WBC 4.51 x 103/µL (50% neutrophils, 34% lymphocytes, 14% monocytes, 2% eosinophils, 1% basophils), hemoglobin 13.2 g/dL, hematocrit 36.8%, platelet 188 x 103/µL. Routine chemistry was normal. Liver biopsy obtained on 07 Oct 2010 showed mild steatosis with minimal inflammation and possible cirrhosis. The patient initiated metreleptin treatment on 22 Feb 2011 based on severe insulin resistance and significant liver disease with possible cirrhosis on liver biopsy. The patient presented to the NIH on 12 Dec 2012 for an unscheduled visit for evaluation of a mass around her right breast (two week history). She was found on exam to have a visible mass just inferolateral to the right lower quadrant of the right breast. The overlying skin showed a very slight purplish color change. The skin could not be lifted off the mass completely but was also not puckered upon elevation of the breast. On palpation, the mass measured about 5 by 4 cm and was minimally tender. It was not fixed but motion was relatively restricted. There was one solitary 1 cm diameter right axillary lymph node noted on palpation, which was shotty, fairly mobile, nontender, and not fixed. The CBC on 12 Dec 2012 showed WBC 10.9 x 103/µL (69% neutrophils, 19% lymphocytes, 6% monocytes, 4% eosinophils, 1% basophils), hemoglobin 11.9 g/dL, hematocrit 35.1%, platelet 460 x 103/µL). A magnetic resonance imaging scan showed an ovoid heterogeneously enhancing mass in the right anterolateral chest that was separate from breast tissue, measuring 3.4 x 3 x 1.5 cm, with right internal mammary lymphadenopathy but no axillary lymphadenopathy. On 13 Dec 2012, two core needle biopsies of the mass were performed. Pathology results available on 20 Dec 2012 showed anaplastic large cell lymphoma (ALCL) that was CD30 positive and stained positive for ALK (anaplastic lymphoma kinase), indicating a T-cell lymphoma. Molecular diagnostics of the core biopsy showed a clonal T-cell population consistent with the diagnosis of ALCL. Fluorescent in-situ hybridization demonstrated the ALK rearrangement present in 89% of cells (normal <10%). The patient returned home after the biopsy with arrangements to return for staging and possible excisional biopsy. Metreleptin therapy was ongoing at discharge. On (b) (6) (b) (6), the patient was admitted to the NIH for further evaluation. The patient and her mother reported that in the intervening ~2 weeks, since the Dec 12 evaluation at the NIH, the mass had decreased in size. Metreleptin was stopped on (b) (6) and fenofibrate 145 mg once daily was started. On examination by the same physicians who examined her on Dec 12, the mass was still palpable but clearly reduced in size, as was the right axillary lymph node. On (b) (6), a positron emission tomography scan showed mild enhancement of the primary lesion (SUVmax 2.31) and only minimal uptake in the right axilla. Examination of CSF on (b) (6) was negative for malignant cells. Bilateral iliac crest bone marrow biopsies performed on (b) (6) showed normocellular marrow with progressive

trilineage hematopoiesis and no evidence of lymphoma. On (b) (6), the patient underwent excisional biopsy of the mass. The pathology report confirmed the diagnosis of anaplastic large cell lymphoma. Immunohistochemical stains showed rare atypical CD30-positive and ALK-positive cells in a similar distribution. Molecular studies did not show a T cell clone similar to that seen in the core biopsy, most likely secondary to the paucity of neoplastic cells. The event of T-cell lymphoma was reported resolved on 14 Dec 2012. The patient continued participation in the study as of the data cutoff date of 11 Jan 2013. Follow-up information available from the site indicated that on 23 Jan 2013, the patient was readmitted to the NIH for follow-up. On physical exam, she had a new, firm, mobile, non-erythematous, slightly tender mass at the site of the excisional biopsy, measuring 4 by 4.5 cm. MRI with gadolinium contrast demonstrated a non-enhancing, homogeneously T2 hyperintense ovoid lesion, compatible with a seroma versus an evolving hematoma at the site of the excisional biopsy. There was no evidence of residual or recurrent disease – specifically, both the primary tumor and the previously noted internal mammary lymph nodes were no longer visualized. Needle aspiration of the cystic mass was performed on 25 Jan 2013 and flow cytometry of the aspirate was suspicious for a T-cell population. A decision was made to re-start metreleptin therapy due to concern regarding dose-limiting hepatic toxicity of potential chemotherapy for the lymphoma, and metreleptin was reinitiated on 12 Feb 2013.

Reviewer comment: In contrast to the other two cases of T-cell lymphoma, this patient did not have a baseline hematologic abnormalities or a history of autoimmune disease, although AGL might be considered an autoimmune disease (all three cases of T-cell lymphoma occurred in patients with AGL). Metreleptin is not genotoxic, so unlikely to have contributed to the development of lymphoma (ALK-positive); however, whether or not metreleptin could have contributed to tumor promotion in this case remains unknown.

7.6.2 Human Reproduction and Pregnancy Data

Hypothalamic hypogonadism is seen in congenital leptin deficiency; treatment with metreleptin in these patients induces pulsatile luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion at the time of puberty. In lipodystrophy, the hyperinsulinemic state associated with severe insulin resistance is associated with hyperandrogenic features in females.

The following table was taken from a publication that described metreleptin treatment in a subset of patients with generalized lipodystrophy from the NIH.[120] In the female patients described in this publication, it was proposed that metreleptin plays a role in normalizing menstrual function.

Table 85. Examples of Menstrual Function in Female Patients with Generalized Lipodystrophy Before and After Receiving Metreleptin

Menstrual function before and after r-metHuLeptin therapy		
Patient	Baseline menstrual status	12 mo menstrual status
NIH 1	Menses once a year	Regular menses
NIH 2	Primary amenorrhea	Regular menses
NIH 3	Regular menses	Regular menses
NIH 4	Primary amenorrhea	Regular menses
NIH 5	Primary amenorrhea	Regular menses
NIH 6	Hysterectomy without oopherectomy	Hysterectomy without oopherectomy
NIH 8	Irregular menses	Regular menses
NIH 13	Primary amenorrhea	Regular menses
NIH 19	Irregular menses	Regular menses
NIH 20	Irregular menses	Regular menses

Source: Reference 120

Reviewer comment: These data cannot be verified. Given that Patient 90113 was 12 years old prior to starting metreleptin, the diagnosis of "primary amenorrhea" seems premature.

As of the data cutoff for the four-month safety update, four pregnancies were reported among 90 patients enrolled in the trial: two live births (Patients 90105, 90140), one premature labor and delivery of nonviable fetus (Patient 90156), and one miscarriage (Patient 90152).

Two pregnancies were captured as serious adverse events and discussed in Section 7.3.2, Nonfatal Serious Adverse Events. Patient 90105 delivered an infant who required full resuscitation at birth and had complications of shoulder dystocia and Erb's palsy. Patient 90156 experienced premature rupture of the membranes with subsequent fetal death.

The following are descriptions regarding what is known of the other two pregnancies:

- Patient 90140: At study entry (22 May 2007), this was a 14-year-old Native American female with CGL and relevant medical history of acanthosis nigricans, asthma, hepatomegaly, hepatosteatosis, and diabetes. On an unknown date in July 2012, the patient contacted the site and informed them she was approximately 12 to 13 weeks pregnant. The patient's last menstrual period was not provided. At that time, the patient was in her fifth year of metreleptin treatment and was reportedly doing well with control of her metabolic parameters. In the past, when not on metreleptin, the patient reportedly experienced extreme metabolic abnormalities of hypertriglyceridemia and hyperglycemia with high dose insulin requirements (greater than 500 units per day). The investigator felt it would be difficult to maintain normal

metabolic pattern without metreleptin treatment through the pregnancy and there was concern regarding risk of hyperglycemia with respect to the fetus. It was decided to continue metreleptin therapy. On an unspecified date in (b) (6), the patient delivered a baby girl. No further information was provided.

- Patient 90152: At study entry (14 Jan 2009), this was a 30-year-old white female with FPL and relevant medical history of pre-eclampsia, pancreatitis, fatty liver, nonalcoholic steatohepatitis, hepatomegaly, polycystic ovary syndrome, hyperlipidemia, insulin resistance, diabetes, and hypertriglyceridemia. In an October 2010 visit, metreleptin treatment compliance was reportedly less than 25%, TG was greater than 7000 mg/dL and the patient had been reportedly using Nuva Ring birth control for one year. In November 2010, the patient called the lead associate investigator at the site and told her she believed she was pregnant. The patient was told to see her local medical doctor and check fasting TG. The patient did not contact the site until mid-December 2010, at which time the patient told the site she had miscarried and that she had not visited her physician. Documentation in the patient's file for the August 2011 visit included the following information: 'In the past year, the patient reports that she had her second miscarriage, this is the first miscarriage following the birth of her twin girls, who are now age 3. She reports following the miscarriage she underwent a D&C and tubal ligation'. The patient was subsequently removed from the study for noncompliance. Her last dose of study medication is unknown. No further information is available. (Note that the miscarriage was reported only by the patient; the site was not able to obtain medical records to confirm the pregnancy.)

As of the data cutoff for the four-month safety update, no pregnancies were reported in FHA101 (N = 35).

In the metreleptin for obesity ISS (Amgen), one pregnancy was reported in a patient treated with metreleptin. No further information was available.

Reviewer comment: The adverse events associated with these pregnancies are likely a result of the co-morbidities in the mothers; it is unknown whether metreleptin contributed to adverse fetal outcomes in these cases. I have some concern regarding the potential for fetal exposure to maternal antibodies; in particular the theoretical risk of neutralizing antibodies (see Section 7.4.6, Immunogenicity) and a congenital leptin deficiency-like condition developing in children born to a mother treated with metreleptin.

7.6.3 Pediatrics and Assessment of Effects on Growth

Of the 72 patients in the NIH trial, 39 (54%) were less than 18 years of age. The assessment of safety in this patient population is challenging, given the relatively small number of patients, the lack of a control group, and the difference in age, time of

diagnosis, or type of lipodystrophy between groups that might impact risk of adverse events. Overall, higher incidences of adverse events and serious adverse events were reported in adults versus pediatric patients. Higher incidences (differing by three or more patients) of adverse events were reported in pediatric patients (less than 18 years) for the System Organ Classes *Cardiac Disorders* and *Metabolism and Nutrition Disorders*. Within System Organ Classes, most of the differences in adverse events were distributed across different preferred terms, except for the preferred term of abdominal pain (five pediatric patients versus no adults).

Of the 28 patients in the FHA101 trial, only 3 (11%) were less than 18 years of age. This reflects the fact that the majority of patients in FHA101 had FPL, which typically presents at an older age.

Pubertal Status

Age of menarche in girls has been shown to be inversely related to serum concentrations of leptin,[121] and in boys, rising leptin concentrations may signal the onset of puberty.[122]

As noted in Section 7.6.2, Human Reproduction and Pregnancy Data, congenital leptin-deficiency is associated with hypogonadotropic hypogonadism and abnormal pubertal development[123] in addition to hyperphagia and extreme obesity. Leptin-deficient *ob/ob* mice and humans administered recombinant leptin restored fertility[124] and normal puberty.[125] Recombinant leptin in patients with congenital leptin deficiency induces pulsatile luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion at the time of puberty.[126]

By contrast, patients with lipodystrophy (females) demonstrate the hyperandrogenism associated with insulin resistance, akin to the polycystic ovarian syndrome (PCOS).[120] In the NIH trial, at baseline, six (15%) out of 39 pediatric patients had a history of pubertal disorders, two with precocious puberty and four with delayed puberty. Tanner staging and assessment of pubertal development were not collected on case report forms; these data are kept on file at the NIH. The following table from the NIH investigators list pubertal status of the pediatric patients prior to and after metreleptin treatment.

Table 86. Individual Patient Listing of Pubertal Status, NIH Trial Pediatric Patients (N=39)

Pubertal Status	CGL	AGL	FPL	APL
Puberty complete or near complete prior to Metreleptin	90102, 90104, 90105, 90122, 90125, 90127, 90133, 90140, 90142, 90160			
Puberty likely complete prior to metreleptin (based on growth data)	90111, 90137, 90153, 90154	90145	90149	
Precocious puberty prior to metreleptin	90131	90148		
Delayed puberty prior to metreleptin	90124, 90164	90101 90109		
Delayed/stalled puberty after metreleptin	90143	90101		
Normal pubertal onset and/or progression on Metreleptin	90113, 90124, 90130, 90134, 90159, 90164, 90167	90110, 90128, 90144 [1] 90150, 90170		90141
Prepubertal before and after metreleptin (normal for age)	90165, 90168, 90169		90166	

CGL = congenital generalized lipodystrophy; AGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; APL = acquired partial lipodystrophy.

Note: Numbers represent individual patient numbers for the NIH studies.

Patients 90101, 90124, and 90164 are listed twice due to their status prior to and during metreleptin treatment.

[1] At time of study entry, patient was assessed by investigator to have APL. As her disorder progressed, the patient's loss of body fat was assessed by the investigator to be more consistent with AGL (Note on file).

Source: Clinical Safety Update, Table 48

The majority [34 (87%) out of 39] of pediatric patients in the NIH trial either had completed or nearly completed puberty (or likely completed) prior to metreleptin, were pre-pubertal before and after metreleptin (appropriate for age), or had normal pubertal onset and/or progression on metreleptin treatment.

Two patients (90101 and 90143) were noted to have delayed puberty after starting metreleptin. Patient 90101 (17-year-old female with AGL) had complete lack of breast development before and after metreleptin treatment (and eventually had breast implants) and had very little documentation of pubertal status after starting metreleptin. She was also extremely ill with other conditions (including pancreatitis, steatohepatitis, nephropathy), which may have contributed to poor pubertal development. Similarly, Patient 90143 (13-year-old female with CGL) was mid-pubertal at time of starting metreleptin with apparent lack of progression on metreleptin but had little documentation of pubertal status, and also was extremely ill with other conditions (cirrhosis, hepatopulmonary syndrome), which may have contributed to poor pubertal development.

Two patients (90124 and 90164) had delayed puberty prior to metreleptin, but had normal pubertal progression after starting metreleptin.

Only three pediatric patients were enrolled in FHA101. The following observations were made regarding pubertal development for these patients:

- Patient 648001 (9-year-old female) was pre-pubertal on study entry and had accelerated pubertal development after initiating metreleptin treatment (except for trailing breast development).

Reviewer comment: Premature development of puberty is a theoretical concern of metreleptin treatment in pre-pubertal patients. This is the only case of premature puberty reported.

- Patient 648016 (11-year-old male) was starting to undergo puberty at the time of study entry and had evidence of age-appropriate progression on metreleptin treatment.

- Patient 648022 (16-year-old female) had primary amenorrhea with developed secondary sexual characteristics at study entry and achieved menarche after nine months of metreleptin treatment.

Linear Growth

Given leptin's effects on pubertal development and weight, linear growth was assessed in pediatric patients. Each NIH pediatric patient who had at least one growth point post-baseline was categorized into one of three categories of stature (short, normal, or tall) at baseline and whether growth was complete or near complete prior to receiving metreleptin (N = 18, 46%). The majority of NIH patients had normal or tall stature prior to metreleptin.

The following table from the NIH investigators list growth of the pediatric patients prior to and after metreleptin treatment.

Table 87. Individual Patient Listing of Growth Status, NIH Trial Pediatric Patients (N=39)††††††††††††

Growth Status	CGL	AGL	FPL	APL
Short stature prior to metreleptin	90143, 90164	90101 90109		90141
Normal stature prior to metreleptin	90102, 90104, 90124, 90125, 90127, 90128, 90133, 90137, 90140, 90142, 90153, 90154, 90159, 90160, 90165, 90167, 90168	90110 90145 90150 90170	90166	90162
Tall stature prior to metreleptin	90105, 90111, 90113, 90122, 90130, 90131, 90134, 90148, 90149, 90169			90144
Growth complete or near complete prior to metreleptin	90102, 90104, 90105, 90111, 90113, 90122, 90124, 90127, 90128, 90133, 90137, 90140, 90142, 90149, 90153, 90160	90101 90145		
Normal growth on metreleptin	90130, 90143, 90159, 90168, 90169	90109 90170	90166	90144
Growth acceleration on metreleptin	90164, 90167			
Growth deceleration on metreleptin	90131, 90134, 90148, 90154, 90165	90110 90150		90141 90162

CGL = congenital generalized lipodystrophy; AGL = congenital generalized lipodystrophy;
FPL = familial partial lipodystrophy; APL = acquired partial lipodystrophy.
Note: Numbers represent individual patient numbers for the NIH studies.
Patient 90125 was not classified for growth status due to the lack of follow-up data. The patient died of pancreatitis 4 months after starting metreleptin treatment.

Source: Summary of Clinical Safety, Table 49

Of 20 patients with growth pattern assessed pattern (normal, accelerated, or decelerated), nine patients had normal growth, two had accelerated growth, and nine patients had growth deceleration on metreleptin. The sponsor notes that growth deceleration likely represents a normalization (or partial normalization) of rapid growth prior to metreleptin, although the sponsor also provided additional reasons for possible growth deceleration:

- Earlier than average puberty leading to earlier growth spurt, and hence, crossing of growth centiles downward

- Improvement in insulin resistance leading to less hyperinsulinemia driving excessive growth

†††††††††††† There are a number of errors in this table. Patient 90128 has AGL, not CGL. Patient 90144 was apparently re-categorized as having AGL rather than APL. Patient 90148 has AGL, not CGL. Patient 90149 has FPL, not CGL. Patient 90162 has AGL, not APL. I am unable to verify the growth data on this table, given that these data were not captured on case report forms.

- Metreleptin-induced weight loss leading to failure of linear growth, which did not appear to be the case for most patients

Reviewer comment: I am unable to verify whether any or all of the possibilities may be true for any individual patients, as these data were not provided. Note that patient 90141 (10-year-old female with APL) had short stature at baseline and growth deceleration on metreleptin. No further details were provided, but this finding was not reported as an adverse event. No patients with tall stature at baseline had accelerated growth on metreleptin.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the NIH studies, there were four reports of acute pancreatitis (5.6%) with discontinuation of, and/or noncompliance with, metreleptin treatment. All four patients had a prior history of pancreatitis and hypertriglyceridemia. Three of the four reports were deemed serious, and all four were assessed as unrelated to metreleptin.

Reviewer comment: Although some of these case reports did not provide comprehensive documentation of rapid increase in TG in the setting of abrupt discontinuation of metreleptin (as discussed in Section 7.3.5, Submission Specific Primary Safety Concerns), it is plausible that in patients at increased risk for pancreatitis because of severe hypertriglyceridemia who have substantial improvements in hypertriglyceridemia with metreleptin therapy may have an increased risk of acute pancreatitis if metreleptin therapy is interrupted.

7.7 Additional Submissions / Safety Issues

The sponsor was asked to provide data that supported the recent (March 2013) metreleptin approval in Japan for treatment of lipodystrophy; these data were submitted as a safety information amendment to the BLA. Shionogi Inc. licensed development rights to metreleptin for treatment of lipodystrophy in Japan, Taiwan, and South Korea from Amylin and was solely responsible for the Japanese development program.

In Japan, trial KUTR-003-0 was initiated by Kyoto University in patients with lipodystrophy. Information from the US NIH clinical trials (991265/20010769) was used to support its use in this population. KUTR-003-0 was an open-label dose-escalating trial that enrolled 11 patients with lipodystrophy and was ongoing at the time of Japanese NDA submission. Subsequently, another open-label dose-escalating trial (KUTR-003-1) in four patients with lipodystrophy was initiated by Kyoto University for the duration of 20 weeks. This trial was concluded in April 2012. The types of lipodystrophy were not reported.

Patients from both of trials were given the opportunity to continue metreleptin therapy in a new open-label fixed-dose trial, called 'Advanced medical study' (KUTR-003-2) at three institutions, including Kyoto University.

Trial Name: design [Trial No.]	No. of Patients Subjects [a)]	Dose/Administration	Administration Period	Efficacy Evaluation Items
Physician-oriented clinical study [KUTR-003-1]: non-blinded dose escalation	4	Males: 0.01, 0.02, 0.04 mg/kg Females (<18 years) : 0.015, 0.03, 0.06 mg/kg Females (≥18) : 0.02, 0.04, 0.08 mg/kg Administration QD SC	20 weeks	Glucose metabolism: HbA1c, fasting glucose, fasting insulin Lipid metabolism: triglycerides Liver function: ALT, AST
Clinical Research Study [KUTR-003-0]: non-blinded dose escalation	11	Males: 0.01, 0.02, 0.04 mg/kg Females (<18 years): 0.015, 0.03, 0.06 mg/kg Females (≥18): 0.02, 0.04, 0.08 mg/kg Year 1: BID SC After year 1: QD SC	1 year + continuing administration	Glucose metabolism: HbA1c, fasting glucose, fasting insulin Lipid metabolism: triglycerides Liver function: ALT, AST
Advanced Medical Study [KUTR-003-2]: non-blinded fixed dose	12	Males: 0.01, 0.02, 0.04 mg/kg Females (<18 years): 0.015, 0.03, 0.06 mg/kg Females (≥18): 0.02, 0.04, 0.08 mg/kg	Continuing administration	

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-1

Item	Physician-oriented clinical study	Clinical research study	Advanced medical study
Number of subjects	4	11	12
Administration period for safety evaluation	136－142 days	125－3209 days	3－13 months [1] 12－22 months [2]
Sex (percentage of females [%])	3 females (75.0)	8 females (72.7)	8 females (66.7)
Age (year)	14.5 (7.5)	22.2 (8.1)	22.0 (8.3)
Height (cm)	148.78 (20.73)	157.5 (8.8)	154.57 (13.88)
Weight (kg)	37.850 (11.919)	46.5 (12.7)	40.15 (10.84)

[1] Period between the start of the advanced medical study and the data cut-off date (31 December 2011)

[2] Period between the start of the advanced medical study and the data cut-off date (30 September 2011)

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-2

One death and one adverse event leading to discontinuation of metreleptin were briefly described.

- Patient 10 was a 35-year-old female (unknown form of lipodystrophy) with history of hypertension, hypertriglyceridemia, hyperuricemia, hepatic steatosis, diabetes mellitus, diabetic neuropathy, diabetic retinopathy, and pancytopenia. The patient was treated with the following doses of metreleptin: 0.9 mg for 34 days, 1.8 mg for 34 days, and 3.4 mg for 726 days. On day 791 (of 794 days) of treatment, the patient experienced an adverse event of bile duct cancer. She reportedly died of the bile duct cancer, although details were not provided.

- Patient 8 was a 33-year-old female (unknown form of lipodystrophy). A decrease in the patient's white blood cell count from 3000/μL to 1000/μL was noted, leading to discontinuation of metreleptin (in one area of the patient information, it states this occurred 23 days after starting treatment, in another 1.5 months after starting treatment). For the subsequent two months, the patient was hospitalized and followed up, without apparent improvement in white blood cell counts.

Reviewer comment: It is noted that patient 10 had pancytopenia at baseline, and patient 8 developed leukopenia; it is unclear whether this finding is part of the natural history of the lipodystrophy seen in Japan, or if these patients had AGL. As noted in Section 7.6.1, Human Carcinogenicity, hematological findings have been described with patients with lipodystrophy (AGL) and in some cases may be a risk factor for the development of lymphoma.

The sponsor was also asked to provide safety information from worldwide experience with metreleptin from other investigational and compassionate-use programs. A total of 407 patients have been exposed to metreleptin in these programs.

Table 88. Investigator-Initiated Trials and Compassionate-Use Treatment with Metreleptin

Study	Patient Population	Number of Metreleptin-Treated Patients
Investigator-initiated Trials		
Lipodystrophy (LD) **[1]**	LD patients	83 [2]
Other Indications	Rabson-Mendenhall, HIV-associated LD, obesity, NASH, HA, type 1 DM, healthy subjects	255 [3]
Named Patient Program (Compassionate Use)		
LD **[1], [2]**	LD patients	51 [4]
Primary Leptin Deficiency	Congenital leptin deficient patients	18

LD = Lipodystrophy; NASH = non-alcoholic steatohepatitis; HA = hypothalamic amenorrhea; DM = diabetes mellitus.

[1] Ongoing studies or ongoing treatment, except completed IIT with C. Levy-Marchal as principal investigator.
[2] Number of subjects as of January 2013.
[3] Studies completed except for Rabson-Mendenhall.
[4] Does not count LD patients who initiated metreleptin treatment through other studies (e.g. NIH 991265/20010769, IITs).
Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-5

Forty-nine patients reported a total of 74 serious adverse events (17 compassionate-use, 57 investigator-initiated trials). No serious adverse events were reported from trials in healthy individuals, or in patients with type 1 diabetes, Rabson-Mendenhall, or hypothalamic amenorrhea.

Table 89. Serious Adverse Events of Special Interest from Compassionate-Use and Investigator-Initiated Trials [1],[2]

SUBSET OF SAEs MEETING CRITERIA OF AE OF SPECIAL INTEREST	Number of Serious Adverse Events [1], [2]			
	LD (Excluding HIV-Related)	HIV-related LD	Obesity	Total
Category Preferred Term				
All Events	**22**	**1**	**2**	**25**
Cancer, Including Hematological Malignancies	**1**	**1**	**1**	**3**
Breast cancer	1	0	0	1
Squamous cell carcinoma of the tongue	0	1	0	1
Thyroid cancer	0	0	1	1
Renal Adverse Events	**2**	**0**	**0**	**2**
Diabetic nephropathy	1	0	0	1
Tubulointerstitial nephritis	1	0	0	1
Pancreatitis	**5**	**0**	**0**	**5**
Pancreatitis	3	0	0	3
Pancreatitis acute	2	0	0	2
Liver-Related Adverse Events	**0**	**0**	**1**	**1**
Hepatic enzyme increased [3]	0	0	1	1
Cardiovascular Adverse Events	**9**	**0**	**0**	**9**
Acute myocardial infarction	1	0	0	1
Cerebrovascular accident	1	0	0	1
Chest pain	1	0	0	1
Heart transplant	1	0	0	1
Hypertension	1	0	0	1
Myocardial infarction	1	0	0	1
Palpitations	1	0	0	1
Pericardial effusion	1	0	0	1
Peripheral artery bypass	1	0	0	1
Hypoglycemia	**5**	**0**	**0**	**5**
Hypoglycemia	2	0	0	2
Hypoglycemia neonatal	1	0	0	1
Hypoglycemic seizure	2	0	0	2

[1] Summary excludes investigator-sponsored trial 991265/20010769 at NIH.
[2] No SAEs of special interest were reported from IITs in healthy subjects, Rabson-Mendenhall patients, hypothalamic amenorrhea patients, type 1 diabetes patients, or non-alcoholic steatohepatitis (NASH) in LD patients.
[3] Blinded study drug (unknown if metreleptin vs. placebo administered).

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-7

8 Postmarket Experience

No information regarding the postmarketing experience of metreleptin in Japan (approved for a lipodystrophy indication in Mar 2013) was provided in the BLA. To my knowledge, no other country has approved metreleptin for marketing for any condition.

9 Appendices

9.1 Literature Review/References

Literature was referenced throughout the document. See the list of references at the end of the document.

9.2 Labeling Recommendations

A detailed labeling review was conducted separately.

9.3 Advisory Committee Meeting

The Endocrinologic and Metabolic Drugs Advisory Committee convened on 11 Dec 2013 to discuss this application. Questions to the committee, discussion, and voting results as captured in the summary minutes[127] are below:

(b) (4)

3 Pages Have Been Withheld In Full Immediately Following This Page. These Pages Are Included In The FDA Advisory Committee Documents. Please Refer To www.fda.gov/AdvisoryCommittees

(b) (4)

9.4 Protocol Summaries

Original Protocol 991265

Objectives

Core Protocol

1. To determine if metreleptin can be safely administered to a group of patients with generalized lipodystrophy

2. To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with generalized lipodystrophy

Studies at NIH

1. To determine if metreleptin treatment will ameliorate lipid deposition in liver and muscle of patients with lipodystrophy

2. To determine if metreleptin treatment will ameliorate hypogonadotropic hypogonadism seen in some patients

Studies at UTSW

1. To determine if insulin sensitivity will improve with metreleptin treatment in patients with lipodystrophy

Entry Criteria

Inclusion Criteria

1. Males and females > 14 years of age

2. Clinically-significant lipodystrophy, identified by the study physician during the physical examination as an absence of fat outside the normal variation and/or identified as a disfiguring factor by the patient

3. Circulating leptin levels < 4.0 ng/mL in females and < 3.0 ng/mL in males on at least 2 occasions obtained from 3 pooled samples

4. Presence of at least one of the following metabolic abnormalities:

    a. Presence of diabetes as defined by the 1997 ADA criteria
        i. Fasting plasma glucose ≥ 126 mg/dL, or
        ii. 2-hour plasma glucose ≥ 200 mg/dL following a 75 gram oral glucose load, or
        iii. Diabetic symptoms with a random plasma glucose ≥ 200 mg/dL

    b. Fasting insulin > 30 µU/mL

    c. Fasting hypertriglyceridemia > 200 mg/dL

Exclusion Criteria

1. Pregnant women, women in their reproductive years who do not use an effective method of birth control, women currently nursing or lactating within 6 weeks of having completed nursing

2. Persons unable to provide informed consent

3. Known liver disease due to causes other than non-alcoholic steatohepatitis

4. Current alcohol or substance abuse

5. Psychiatric disorder impeding competence or compliance

6. Active tuberculosis

7. Use of anorexigenic drugs

8. Other condition, which in the opinion of the clinical investigators would impede completion of the trial

9. Subjects who have a known hypersensitivity to *E. coli*-derived proteins

Study Design and Methods: Core Study

General Design

4-month open-label trial

Screening

1. History and physical examination: Special attention directed to details listed in the exclusion criteria. The degree of acanthosis nigricans, lipoatrophy / lipodystrophy, and hirsutism / virilization will also be recorded.

2. Laboratory parameters: Fasting glucose, fasting leptin, liver function tests, fasting lipids, complete blood count, fasting insulin, and HbA1c.

Study Assessments

1. Baseline laboratory tests: electrolytes, BUN, creatinine, LDH, CPK, AST, ALT, bilirubin, alkaline phosphatase, calcium, magnesium, albumin, protein, thyroid function tests, urinalysis, urine pregnancy test (if applicable), CBC with differential

2. Metabolic tests: oral glucose tolerance test, insulin tolerance test, resting metabolic rate, lipid profile

3. Estimation of body fat: BMI, skin-fold measurements, leptin concentrations

4. Serum and plasma to be stored for hormone and cytokine evaluations

Drug Dosage and Administration

Metreleptin injections will be injected subcutaneously at doses predicted to achieve 50%, 100%, and 200% of normal leptin concentrations based on a “normal body fat” of 30% in females and 20% in males. The dose of metreleptin needed to achieve a normal leptin concentration (100%) for female children (14 to less than 18 years and adult females will be 0.03 mg/kg and 0.04 mg/kg lean body weight, respectively. The dose of metreleptin needed to achieve a normal leptin concentration (100%) for all males will be 0.02 mg/kg lean body weight.

Patients will be started at 50% of this predicted dose and maintained at this dose for one month. The dose will then be increased to 100% of predicted dose for another month. If this is tolerated, then the dose will be increased to 200% of predicted dose. Thereafter, patients will be maintained at this dose until the end of the study period (4 months). If patients do not tolerate a higher dose, they can continue the trial at the dose they tolerated.

The total daily dose will be administered via subcutaneous injections in two equally divided doses (12 hours apart).

Study Sequence

1. Week 1 (Days 1-7):
    a. Admission to research centers
    b. History and physical examination
    c. RMR after 12-hour fast
    d. Fasting baseline blood work
    e. ITT
    f. OGTT
    g. Center-specific testing
    h. Glucose before each meal and at bedtime
    i. 24-hour glucosuria and other 24-hour urine studies
    j. Begin metreleptin injections on Day 7, with 48-hour observation
    k. Education on in-home glucose monitoring and self-injection techniques

2. Weeks 2-3 (Days 7-21):
    a. Previous glucose-lowering therapies (if applicable) will be tapered to prevent hypoglycemia, if necessary

3. Week 4 (Days 22-28):
    a. Return to research centers for repeat of baseline testing
    b. Dose of metreleptin will be increased to 100% of predicted dose in dose is tolerated; patients will be withdrawn if they cannot tolerate 50% predicted dose

4. Weeks 5-8 (Days 29-56):
    a. Patients remain on 100% predicted dose
    b. Glucose monitoring

5. Week 8 (Days 50-56):
    a. Return to research centers for repeat of baseline testing
    b. If patients are tolerating 100% predicted dose, increase to 200% predicted dose

6. Weeks 9-16 (Days 57-112):
    a. At the end of 12 weeks, patients will have blood drawn at their local doctors' offices to check liver function tests and complete blood counts
    b. At the end of 16 weeks, patients will return to the research centers for repeat of baseline testing

Safety Monitoring

Safety will be assessed with physical exam at each visit, weekly symptom sheets and glucose logs, and monthly determinations of liver and kidney function tests, CPK, and complete blood count.

Study Schema

Tests	**Baseline**	**Mo 1**	**Mo 2**	**Mo 4**
Leptin concentrations	X	X	X	X
Fasting glucose	X	X	X	X
Fasting insulin	X	X	X	X
Fasting lipids	X	X	X	X
Additional chemistry	X	X	X	X
Hematological tests	X	X	X	X
Resting energy expenditure	X	X	X	X
Immunological tests*	X	X	X	X
Bone turnover*	X	X	X	X
Insulin tolerance test	X	X	X	X
OGTT	X	X	X	X
IVGTT*	X			X
TRH/LHRH test*	X			X
CRH test*	X			X
Body fat analysis				
MRI*	X	X	X	X
Anthropometrics	X	X	X	X
Liver fat analysis (MRI)*	X	X	X	X
Pelvic ultrasound*	X			X
Food questionnaire	X	X	X	X
Exercise questionnaire	X			X
Liver biopsy (patients with documented liver abnormalities)*	X			X
Muscle biopsy (optional)*	X			X

Liver and muscle TG and G-6-P at Yale (optional)	X			X
* NIH site-specific studies				

Source: BLA 125390, 15 Dec 2010 submission, Protocol 991265 p35

Secondary Outcome Measures for UTSW

1. Insulin sensitivity
2. Muscle and liver TG content (NMR)

Sample Size

Based on preliminary data in a cross-sectional study, the mean ± SD HbA1c data for eight patients with generalized lipoatrophy was 9.9 ± 2.2%. Assuming a 1.5% decrease in HbA1c over a period of four months, ten patients would be required for 80% power and an alpha of 5%.

Based on this cross-sectional study, the mean ± SD fasting TG data for eight patients with generalized lipoatrophy was 2200 ± 900 mg/dL. Assuming a 660 mg/dL (or 30%) decrease over a period of four months, 12 patients would be required for 80% power and an alpha of 5%.

Therefore, a minimum of 12 patients with both hyperglycemia and hypertriglyceridemia would be needed. Twenty patients between the two centers will be recruited to allow for patients who display only one of the metabolic abnormalities.

Protocol 991265 Amendment 1

The protocol was amended to treat patients for a total of eight months and monitor metabolic control.

Protocol 991265 Amendment 2

After eight months of treatment, patients were offered a withdrawal trial, which would require an inpatient admission and controlled diet. Afterwards, leptin therapy would resume in a long-term extension trial with follow-up visits every six months.

Protocol 20010769 (original)

Objectives

- To determine if metreleptin can be safely administered to a group of patients with lipoatrophy and low leptin levels starting at age 5 and older

- To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with lipoatrophy and leptin deficiency starting at age 5 and older

- To determine if metreleptin treatment will be effective in patients with less severe forms of lipodystrophy (as evidenced by slightly higher circulating leptin concentrations) in terms of improving insulin sensitivity, triglyceride levels, and non-alcoholic steatohepatitis

Entry Criteria

Inclusion Criteria

1. Males and females > 5 years

2. Clinically significant lipodystrophy, identified by the study physician during the physical examination as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient

3. Circulating leptin levels < 6.0 ng/mL in females and < 3.0 ng/mL in males on at least two occasions obtained from pooled samples

4. Presence of at least one of the following:

    a. Diabetes as defined by the 1997 ADA criteria
        i. Fasting plasma glucose ≥ 125 mg/dL, or
        ii. 2-hour plasma glucose ≥ 200 mg/dL following a 75-gram oral glucose load, or
        iii. Diabetic symptoms with a random plasma glucose ≥ 200 mg/dL

    b. Fasting insulin ≥ 30 µU/mL while not on exogenous insulin therapy

    c. Fasting TG > 300 mg/dL

Exclusion Criteria

1. Pregnant women, women in their reproductive years who do not use an effective method of birth control, women currently nursing or lactating within 6 weeks of having completed nursing

2. Persons unable to provide informed consent

3. Known infectious liver disease

4. Current alcohol or substance abuse

5. Psychiatric disorder impeding competence or compliance

6. Active tuberculosis

7. Use of anorexigenic drugs

8. Other condition, which in the opinion of the clinical investigators would impede completion of the trial

9. Subjects who have a known hypersensitivity to *E. coli*-derived proteins

Study Design and Methods

Baseline and study measures are similar to those outlined in protocol 991265. This protocol was only conducted at the NIH site.

The study schema between 1-4 months was as outlined above.

Study Schema: Months 4-12

Tests	Mo 4	Mo 6	Mo 8	Mo 12
Leptin concentrations	X	X	X	X
Fasting glucose	X	X	X	X
Fasting insulin	X	X	X	X
Fasting lipids	X	X	X	X
Additional chemistry	X	X	X	X
Hematological tests	X	X	X	X
Resting energy expenditure	X	X	X	X
Immunological tests	X	X	X	X
Bone turnover	X	X	X	X
Insulin tolerance test	X	X	X	X
OGTT	X	X	X	X
IVGTT	X		X	X
TRH/LHRH test	X			
CRH test	X			
Body fat analysis				
MRI	X	X	X	X
Anthropometrics	X	X	X	X
Liver fat analysis (MRI)	X	X	X	X
Pelvic ultrasound	X		X	X
Food records	X	X	X	X
Exercise questionnaire	X		X	X
Quality of life assessment	X		X	X
Liver biopsy (patients with documented liver abnormalities)	X			
Muscle biopsy (optional)	X			
Liver and muscle TG and G-6-P at Yale (optional)	X		X	

Source: BLA 125390, 15 Dec 2010 submission, Protocol 991265 p35

Protocol 20010769: Amendments

Amendment 1 (2003)

- Sample size increased from 20 to 40 patients.

- Patients evaluated every four months during the first year of therapy (compared to more frequent intervals in the initial protocol). Treatment duration was extended from 12 months to beyond 12 months. If the patient showed no improvements after one year, the study medication was to be withdrawn. If the patient did show improvement, the patient was to be evaluated every six months during the second year of treatment. Following the second year, extending the treatment period on an annual basis was to be left up to the patient, PI, and Amgen Inc.

Reviewer comment: Note that no patients were withdrawn due to lack of efficacy.

- Following the Month 2 visit, patients were to remain on 200% of the predicted dose until the Month 8 visit (vs. Month 12 visit in the original protocol). If the patient's response was not optimal following the Month 8 visit, the dose could be increased up to 300% replacement.

- The dose of metreleptin was changed from "increases of 0.01 mg/kg/day with each increase tested for a minimum of 3 weeks" to "the dose of metreleptin can be increased after the 8-month follow up".

- The protocol was changed from evaluating leptin therapy in "a similar group of patients" to "in children and adult patients"

- Evaluation of cumulative changes from baseline was changed from "evaluation at 1 year" to "evaluation during the study period".

Amendment A (2006)

- Maximum daily dose of metreleptin increased from 0.12 mg/kg/day to 0.24 mg/kg/day. A new dosing chart was included in the Appendix of the amendment.

- Patients were to switch from "BID dosing" to "BID dosing followed by once daily dosing (same total daily dose) of metreleptin after 1 year of BID therapy". If significant decrease in metabolic control (i.e., increase in HbA1c >1% and/or increase in fasting triglycerides >200 mg/dL) occurred after switching to QD dosing, dosing was to revert back to BID dosing.

- The rights to metereleptin were transferred from Amgen Inc. (Amgen) to Amylin Pharmaceuticals Inc (Amylin).

- Follow up liver biopsies were changed from “8 months after starting leptin therapy” to “at least 12 months after starting leptin therapy”.

Amendment B (2007)

- The sample size was increased from 40 to 75 patients.

- Water for reconstitution was changed from “previous sterile water for reconstitution (vials considered single use after reconstitution)” to bacteriostatic water for reconstitution of metreleptin allowing multiple doses to be used from a single vial (up to 3 days).”

- Collection of three morning fasting samples to be pooled for leptin concentrations was changed to collection of just one sample for measurement of leptin.

Amendment C (2008)

- Metreleptin was changed from “BID dosing followed by once daily dosing (same total daily dose) of metreleptin after 1 year of BID therapy” to “Initiate at QD dosing to improve compliance as metabolic effect did not appear to be compromised; patients were to be switched to BID dosing only if dose and patient treatment warranted.”

- Sterile water could continue to be used for reconstitution of metreleptin in those patients on daily doses of metreleptin such that ability to use multiple doses from same vial was not relevant.

- Upper limit of baseline leptin level for inclusion criteria was increased from 6 ng/mL to 12 ng/mL for females and from 4 ng/mL to 8 ng/mL for males.

Amendment D (2009)

- Lower limit on age inclusion criteria was lowered from 5 years of age to 6 months of age (only sterile water can be used for reconstitution in patients under 3 years of age)

- Inclusion criteria were altered to allow for postprandial TG > 500 mg/dL in cases where fasting was not clinically indicated (e.g., in infants)

- Exclusion criteria modified to exclude patients with acquired lipodystrophy with hematological abnormalities such as neutropenia or lymphadenopathy

- Note the updated objectives:

    - To determine if metreleptin can be safely administered to a group of patients with lipoatrophy and low leptin levels starting at age six months

    - To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with lipoatrophy and leptin deficiency starting at six months

    - To determine in metreleptin treatment will be effective in patients with less severe forms of lipodystrophy (as evidenced by slightly higher circulating leptin concentrations) in terms of improving insulin sensitivity, triglyceride levels and non-alcoholic steatohepatitis (as assessed by both liver volume, serum markers of liver inflammation and function, and liver histopathology)

    - To determine effective dose ranges of metreleptin for patients with lipodystrophy

    - To devise effective anti-diabetic and lipid-lowering regimens concomitantly with leptin for patients with lipodystrophy and leptin deficiency starting at age six months

Treatment Protocol FHA101 (research version: addendum to amendment 3)

Objectives

Primary

- To provide metreleptin under a treatment protocol to patients with lipodystrophy that is associated with diabetes mellitus and/or hypertriglyceridemia

Secondary

- To monitor the safety and tolerability of metreleptin

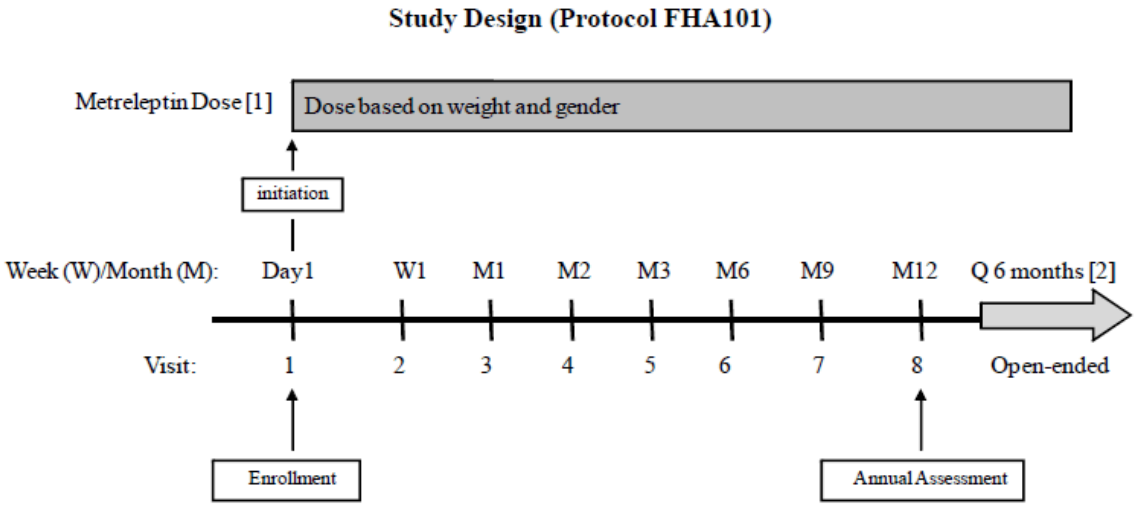
- To collect information of the efficacy of metreleptin as assessed by its effects on fasting TG, HbA1c, and fasting glucose

Protocol Design

- Open-label and open-ended and will continue until the study is terminated for administrative or safety reasons

- Dosing
    - Patients will self-inject metreleptin subcutaneously according to the dosing regimen outlined below
    - Metreleptin injections may be administered by a parent, guardian, or care-giver to subjects needing assistance, including young children
    - The recommended starting dose of metreleptin is 0.02 mg/kg BID for 1 month, to be increased to a recommended target dose of 0.04 mg/kg BID
    - The recommended target dose can be increased in 0.02 mg/kg increments up to 0.12 mg/kg BID (or 0.24 mg/kg daily) if the primary treating physician judges that the patient's metabolic improvement is suboptimal
    - The target dose of metreleptin may be reduced in 0.02 mg/kg decrements to 0.02 mg/kg BID or even lower to 0.01 mg/kg BID, if a patient experiences side effects such as excess weight loss or injection-site reactions
    - After subjects are on a stable metreleptin dose and desired improvements in metabolic parameters are observed, subjects may transition from a BID to a QD dosing regimen without altering the total daily dose
- The investigators should schedule follow-up visits with their patients according to the schedule of recommended visits, to monitor each patient's condition and collect basic information regarding treatment efficacy, safety, and tolerability. More frequent visits may be scheduled based on the clinical judgment of the investigator.
    - Eligible patients will be enrolled into the protocol on Day 1 and will be asked to return to the clinical protocol site in approximately 1 week for Visit 2 (Week 1)
    - Patients should visit their treating physician (the investigator) at least monthly during the first 3 months, and every 3 months thereafter during the first year of treatment
    - Investigators are encouraged to schedule an annual assessment visit approximately 12 months after initiation of metreleptin, at which point the patient and investigator will determine the frequency of subsequent visits as well as the dosing regimen during continued metreleptin treatment
    - Following 1 year of treatment, subject visits should be scheduled every 6 months or more frequently as deemed appropriate by the investigator

Figure 34. FHA101 Study Design



[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.

Source: BLA 125390, Clinical Efficacy Update 27 March 13 Submission, Appendix 2

Study Population

Inclusion Criteria

- Male or female ≥ 5 years old at baseline

- If female of childbearing potential, must:
  - Not be breastfeeding
  - Have a negative pregnancy test result at baseline
  - Practice appropriate birth control

- Has physician-confirmed lipodystrophy as defined by evidence of generalized (whole body) or partial (limbs) loss of body fat outside the range of normal variation

- Has been diagnosed with at least one of the following:
  - Diabetes mellitus
  - Hypertriglyceridemia (TG > 200 mg/dL)

- Has a calculated renal clearance > 40 mL/min; subjects with a calculated renal clearance ≤ 40 mL/min may be included; however, the Medical Monitor should be contacted for dose adjustment

Exclusion Criteria

- Has been diagnosed with HIV infection
- Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being
- Has acquired lipodystrophy and clinically significant hematological abnormalities (such as neutropenia and/or lymphadenopathy)
- Has known infectious liver disease
- Has known allergies to *E. coli*-derived proteins or hypersensitivity to any component of study treatment

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/s/

JULIE K GOLDEN
02/23/2014

ERIC C COLMAN
02/24/2014

EXECUTIVE SUMMARY OF CLINICAL REVIEW

Reviewer: Julie Golden

Lipodystrophy is a group of rare disorders characterized by the loss of body fat. The extent and distribution of fat loss to a large extent determine the associated co-morbidities. Ectopic fat accumulation in muscle and liver likely contributes to the severe insulin resistance and associated diabetes mellitus and hypertriglyceridemia seen in many patients with lipodystrophy. Some forms of lipodystrophy are genetic in basis and some are acquired; acquired forms are often associated with autoimmune diseases. The forms of lipodystrophy referred to in this review are congenital generalized lipodystrophy (CGL), acquired generalized lipodystrophy (AGL), familial partial lipodystrophy (FPL), and acquired partial lipodystrophy (APL). (Patients with human immunodeficiency virus (HIV)-associated lipodystrophy were not studied in this development program.)

Leptin is a hormone primarily expressed in adipose tissue and, therefore, is relatively deficient in patients with lipodystrophy. Circulating leptin concentrations strongly correlate with body fat stores. In one paper, the mean (SD) serum leptin concentration in 139 obese individuals was 31.3 (24.1) ng/mL compared with 7.5 (9.3) ng/mL in 136 normal-weight individuals ($p < 0.001$).[1] The normal physiological function of (low) leptin is to act as a signal of starvation or fasting when fat stores are low; in low leptin conditions, appetite is increased and reproductive axes and immunological functions are diminished.

Soon after the discovery of the leptin gene in 1996, an analog of human leptin (metreleptin) was developed and evaluated for a number of conditions, including obesity and lipodystrophy. Metreleptin was originally studied for lipodystrophy (since 2000) in a small cohort of patients at the National Institutes of Health (NIH), who demonstrated decreases in hyperphagia and dramatic improvements in glucose metabolism and triglycerides, as well as shrinking of enlarged livers. Because of the compelling findings in this small cohort, it was determined that the use of a placebo control in this patient population would be unethical and, therefore, the trial continued as a single-arm, open-label protocol. The research protocol has been ongoing since that time; the total number of patients available for efficacy and safety evaluations in the most recent data cutoff was 72. Importantly, protocol amendments over time changed the inclusion criteria to include patients with higher baseline leptin concentrations and younger patients. These changes have resulted in the enrollment of more patients with partial forms of lipodystrophy and patients with less severe metabolic abnormalities at baseline.

In 2008, a treatment IND was opened by the sponsor to provide expanded access to metreleptin for patients with lipodystrophy. A total of 28 patients had data available for efficacy and safety evaluations in the most recent data cutoff. Most of the patients enrolled in this protocol to-date have FPL.

Efficacy Summary

Without a placebo group or adequate historical control, it is challenging to attribute beneficial changes to metreleptin versus improvements in diet or enhanced compliance with concomitant antihyperglycemic or lipid-lowering medications. Furthermore, a substantial amount of missing data, variable duration of therapy, variation in the timing of efficacy assessments, variable and within-trial adjustment of background therapies, compliance that was not systematically documented, and protocol

[1] Considine RV, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. New Engl J Med. 1996; 334:292-5.

changes add to the challenges of isolating the effect of metreleptin on metabolic control in this application. Nevertheless, a subgroup of patients appears to have achieved benefits from metreleptin that would be unlikely to have been achieved spontaneously: patients with generalized lipodystrophy (congenital or acquired) with severe insulin resistance resulting in diabetes mellitus and / or severe hypertriglyceridemia not adequately controlled with other therapies. The apparent response of this subgroup overall is consistent with that of the initial small group of patients from the trial described above, and further, is consistent with the mechanism of action of leptin. Metreleptin appears to treat the insulin resistance of lipodystrophy; to the extent diabetes and hypertriglyceridemia are the result of insulin resistance, metreleptin treatment is associated with improvements in, and in some cases normalization of, metabolic control. The table below highlights the differences at 12 months in the key efficacy endpoints of hemoglobin (Hb) A1c, fasting plasma glucose (FPG), and triglycerides (TG) between the patients with generalized lipodystrophy and patients with partial lipodystrophy. In addition, the improvements are accentuated in those patients with uncontrolled diabetes mellitus (defined here as HbA1c 7% or greater or FPG 126 mg/dL or greater) or severe hypertriglyceridemia (defined here as TG 500 mg/dL or greater), supporting the drug's efficacy in treating these diseases.

Table 1. Key Efficacy Parameters at Baseline and Month 12 in Generalized and Partial Lipodystrophy: All Patients and Patients with Elevated HbA1c, FPG, and TG; NIH Trials

HbA1c, %	All			Baseline HbA1c ≥ 7%		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	29	8.7 (0.4)	-2.0 (0.3)	24	9.3 (0.3)	-2.4 (0.5)
Partial	21	7.5 (0.5)	-0.4 (0.2)	11	9.2 (0.5)	-1.0 (0.4)
Fasting glucose, mg/dL	All			Baseline FPG ≥ 126 mg/dL		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	31	179.5 (15.9)	-48.3 (16.9)	21	218.6 (17.8)	-82.1 (16.5)
Partial	21	155.8 (19.3)	-32.1 (14.8)	11	220 9 (22.5)	-68.6 (23.2)
TG, mg/dL	All			Baseline TG ≥ 500 mg/dL		
	n	Baseline Median	Δ from baseline at Month 12 Median	n	Baseline Median	Δ from baseline at Month 12 Median
Generalized	30	414.5	-246.5	12	1526.5	-1117.0
Partial	21	357.0	-74.0	7	1237.0	-499.0

The severity of metabolic abnormalities at baseline was more heterogenous in patients with partial lipodystrophy in the NIH trials and, overall, the observed reductions in HbA1c and TG were less than those observed in patients with generalized lipodystrophy. Furthermore, whereas the majority of patients in the NIH trials with generalized lipodystrophy on concomitant anti-hyperglycemic medications at baseline discontinued or had significant reduction in the doses of anti-hyperglycemics at Month 12, a greater proportion of patients with partial lipodystrophy versus generalized lipodystrophy had anti-hyperglycemic medications added to their regimen or doses increased, including two patients with partial lipodystrophy who added insulin to their regimen by Month 12. Similarly, although the majority of patients on lipid-lowering medications at baseline had regimens unchanged at Month 12, the two patients who discontinued all lipid-lowering medication at Month 12 had generalized lipodystrophy, whereas the six patients whose dose of fibrate was increased or who had a lipid-lowering drug added (fibrate or non-fibrate) at Month 12 had partial lipodystrophy.

Because of the smaller reductions in metabolic parameters and confounding by concomitant medications in patients with partial lipodystrophy, it is unclear if a subgroup of patients with partial lipodystrophy can be clearly identified who may benefit from metreleptin. Baseline fasting leptin could be an important factor, particularly given the observation that lipodystrophy patients in earlier versions of the NIH protocol were selected on the basis of low fasting leptin values (originally defined as less than 4 ng/mL in females and less than 3 ng/mL in males) and appeared to have a more pronounced changes in metabolic parameters during metreleptin treatment.

Over the entire NIH cohort, patients with generalized lipodystrophy had mean (SD) fasting leptin of 1.3 (1.1) ng/mL and those with partial lipodystrophy had a value of 4.9 (3.1) ng/mL. The relationship between baseline leptin and changes in metabolic parameters associated with metreleptin treatment was specifically evaluated in patients with partial lipodystrophy who had a wider range of baseline leptin values compared with patients with generalized lipodystrophy who almost all had "low" leptin levels. Across all three endpoints (i.e., HbA1c, FPG, and TG), a greater change from baseline was observed for patients with low baseline leptin concentration in patients with partial lipodystrophy (Table 2). For example, while the average change from baseline in HbA1c at Month 12 was -0.9% for patients with partial lipodystrophy and low leptin levels, it was only -0.1% for patients with partial lipodystrophy and higher leptin levels.

Table 2. Change From Baseline to Month 12 in Key Efficacy Parameters by Leptin Categories; NIH Trials

	Mean (SE) HbA1c (%)			Mean (SE) FPG (mg/dL)			Median TG (mg/dL)		
	N	**Baseline**	**Δ from BL at Mo 12**	**N**	**Baseline**	**Δ from BL at Mo 12**	**N**	**Baseline**	**Δ from BL at Mo 12**
Generalized									
All									
Low leptin	26	8.6 (0.4)	-2.1 (0.3)	28	176 (17)	-48 (18)	28	415	-247
Higher leptin	1	10.1 (na)	-1.6 (na)	1	200 (na)	-134 (na)	1	158	-105
Elevated Baseline	Baseline HbA1c ≥ 6%			Baseline FPG ≥ 126 mg/dL			Baseline TG ≥ 200 mg/dL		
Low leptin	23	9.1 (0.4)	-2.4 (0.3)	18	219 (20)	-87 (18)	20	562	-395
Higher leptin	1	10.1 (na)	-1.6 (na)	1	200 (na)	-134 (na)	-	-	-
Partial									
All									
Low leptin	10	7.6 (0.9)	-0.9 (0.4)	10	178 (33)	-56 (27)	10	609	-237
Higher leptin	11	7.5 (0.5)	-0.1 (0.2)	11	136 (22)	-11 (13)	11	343	-64
Elevated Baseline	Baseline HbA1c ≥ 6%			Baseline FPG ≥ 126 mg/dL			Baseline TG ≥ 200 mg/dL		
Low leptin	6	9.2 (1.0)	-1.6 (0.4)	6	239 (36)	-99 (34)	8	1020	-429
Higher leptin	8	8.1 (0.5)	-0.2 (0.2)	5	199 (26)	-32 (24)	8	358	-65

Safety Summary

Patients with lipodystrophy can present with significant co-morbidities, often as a result of the complications of lipodystrophy (e.g., pancreatitis, atherosclerosis, cirrhosis), or reflecting an underlying autoimmune disease as in the case of many patients with acquired lipodystrophies. It is particularly challenging to assess the safety of metreleptin and adjudicate its role in a variety of adverse events, given the high background incidence of co-morbid disease and the theoretical possibility that metreleptin may exacerbate certain conditions via its activation of the Janus kinase signal transducer and activator of transcription (JAK-STAT) and other intracellular pathways, as well as its effects on the immune system. Safety issues of particular interest in this development program include the following:

- T-cell lymphoma: Three cases of T-cell lymphoma have been reported in patients with AGL in the NIH trials. Two of the cases occurred in patients with hematological disease (neutropenia, lymphadenopathy) at baseline and were on confounding medications, such as G-CSF and erythropoietin. A third patient (13-year-old with AGL) did not have any known hematological disorders or other confounding factors prior to developing lymphoma, aside from the AGL diagnosis. Leptin is a cytokine that exerts its effect by binding to the leptin receptor on cell surfaces and activating the JAK-STAT intracellular pathway. Leptin signaling via JAK-STAT and other pathways promotes cell growth and survival and inhibits apoptosis. Dysregulation of STAT proteins and signalling contributes to the pathogenesis of some malignancies. It is unknown if metreleptin could promote the progression of lymphoma or other malignancies in a patient population that is predisposed to these diseases. Of note, hematological malignancies, including T-cell lymphoma, have been reported in the literature in patients with lipodystrophy not treated with metreleptin.

- Immunogenicity: Metreleptin is highly immunogenic. The majority of patients exposed in clinical trials developed anti-leptin antibodies. Development of binding antibodies is associated with supraphysiological concentrations of circulating leptin, as well as inflammatory injection site adverse events. To some extent, the long-term clinical sequelae of antibody development are unknown. Nevertheless, a number of adverse events associated with the development of antibodies with neutralizing activity, particularly in patients treated with metreleptin in the development program for obesity (not currently active), has highlighted a potential risk for off-label use. Three patients in the obesity program have been identified with the development of neutralizing antibodies. All three patients presented with high antibody titer, low leptin concentrations, and excessive body weight gain (13 kg to 66 kg above baseline body weight). One patient in the lipodystrophy program was recently identified as having developed high-potency, highly reproducible, neutralizing anti-leptin antibodies. This patient, a 19-year-old female with CGL, appears to have had some loss of efficacy (HbA1c) based on the last measured efficacy parameters and, perhaps more significantly, has had five hospitalizations as a result of various bacterial infections over this past summer. Because of the role that leptin plays in the functioning of the immune system, it is theoretically possible that neutralizing antibodies to leptin could have implications for immune functioning (i.e., immunodeficiency), even in patients with very low endogenous leptin. An additional unanswered question related to the development of neutralizing antibodies in the lipodystrophy population is whether a risk of maternal-fetal transfer of neutralizing antibodies exists, and whether a baby born to a mother with neutralizing antibodies could develop a congenital leptin deficiency-like condition.

- Autoimmunity: Leptin activates a number of cell signaling pathways important in T-cell activity and is permissive in cellular proliferation and cytokine production. Therefore, exacerbation of autoimmunity is a theoretical concern, given leptin's role in the immune system. In the NIH trials, adverse events of autoimmune hepatitis and membranoproliferative glomerulonephritis (associated with massive proteinuria and renal failure) exacerbations were seen in some patients with AGL treated with metreleptin. The contribution of metreleptin in these cases is unknown, but appears plausible.

- Other Immune-Related Adverse Events: Other potentially immune-related adverse events in the lipodystrophy trials included urticaria, pruritus, arthralgia, asthma, rash, and facial swelling. (A single anaphylactic reaction was thought likely food-related.) In a summary of five pooled placebo-controlled obesity trials, severe injection site reactions were reported in 0.9% of metreleptin-treated patients versus 0.3% of placebo-treated patients. Other injection-site adverse events occurring

more frequently in metreleptin-treated compared to placebo-treated patients included injection site erythema (10.8% versus 0.6%), injection site inflammation (4.8% versus 0.6%), injection site edema (2.3% versus 0.0%), injection site pruritus (8.0% versus 1.7%), and injection site rash (2.4% versus 0.0%). In the pooled obesity trials, non-injection site reaction adverse events reported as associated with hypersensitivity were experienced by 14% of metreleptin-treated patients versus 8% of placebo-treated patients. A serious adverse event of systemic hypersensitivity occurred in an obesity trial participant.

- Hypoglycemia: Hypoglycemia was the most frequent adverse event reported in the lipodystrophy trials. In the NIH trials, hypoglycemia was reported only in those patients receiving concomitant insulin therapy with or without oral anti-hyperglycemic agents. No severe hypoglycemia events (e.g., requiring the assistance of another individual) were reported. In the treatment protocol, one patient experienced a severe event of hypoglycemia that required assistance from another person. In this trial, most events of hypoglycemia occurred in patients who were receiving concomitant insulin therapy or a sulfonylurea with or without other oral antihyperglycemic agents, except one patient who experienced an event of hypoglycemia while on metformin only. In patients with type 2 diabetes mellitus in the pooled obesity trials, 14.3% of patients on metreleptin and 5.0% of patients on placebo reported hypoglycemia.

- Pancreatitis: Patients with lipodystrophy are predisposed to acute pancreatitis, due to marked hypertriglyceridemia (often defined as TG greater than 1000 mg/dL). In the NIH trials, 16 (22.2%) patients had a medical history of pancreatitis and 4 (5.6%) patients had a history of recurrent pancreatitis. Although some patients treated with metreleptin appeared to have significant improvement in TG concentrations, many patients continued to have high or fluctuating TGs, and adverse events of pancreatitis were seen in the lipodystrophy trials. As there was no control group, and the trials were not powered to detect either an improvement or worsening in pancreatitis, the potential contribution of metreleptin on pancreatitis events in a patient population predisposed to this adverse event is unknown. The sponsor has proposed that patients who developed pancreatitis in the lipodystrophy program were non-compliant or they discontinued or interrupted metreleptin too rapidly with subsequent rebound in serum TG. Of note, in the pooled obesity trials, one patient treated with metreleptin (out of 784) had a serious adverse event of pancreatitis, versus no placebo-treated patients (out of 351).

- Liver-Related Adverse Events: Patients with lipodystrophy who have undergone liver biopsy have been described to fall within the spectrum of non-alcoholic fatty liver disease (NAFLD), from none to inflammation and fibrosis (including cirrhosis), as well as having other liver diseases such as autoimmune hepatitis. Seven patients in the lipodystrophy development program had adverse events related to the liver; all had liver-related abnormalities at baseline. Notably, five out of the seven events occurred in patients with AGL, three of whom had known autoimmune hepatitis at baseline. No patient in the lipodystrophy program met the laboratory criteria for Hy's law (i.e., ALT or AST greater than 3x ULN accompanied by total bilirubin greater than 2x ULN); however, a patient in the NIH trial (18-year-old female with AGL) with a history of cirrhosis died due to progressive end-stage liver disease.

- Nephropathy: Proteinuric nephropathies have been associated with lipodystrophy, and approximately one third of the patients in the lipodystrophy program had a medical history of proteinuria. In the NIH trials, worsening of renal disease (proteinuria or creatinine increases or adverse events relevant to proteinuric nephropathies) was seen in 12 patients, and five of those

patients were known to have ultimately progressed to end-stage renal disease, despite transient improvements in proteinuria in some cases. The contribution of metreleptin to the worsening of underlying renal disease is unknown; however, an effect on autoimmune-related renal disease in patients with AGL appears plausible.

Conclusion

Leptin is an adipose tissue-derived hormone that plays a key role in energy homeostasis. Patients with lipodystrophy have varying degrees of fat loss and therefore varying degrees of leptin deficiency. The lack of adequate storage depots for fat in patients with lipodystrophy lead to its ectopic deposition in tissues such as muscle and liver, which result in metabolic diseases such as insulin-resistant diabetes mellitus, hypertriglyceridemia, and hepatic steatosis. Hyperphagia in these patients likely exacerbates metabolic disease. Replacement or supplementation of leptin with metreleptin appears to improve the metabolic complications of lipodystrophy, although importantly, it does not treat the underlying disorder. Patients with generalized forms of lipodystrophy and significant insulin resistance appear to achieve the best results, including large and, in some cases, sustained improvements in HbA1c and TG, often accompanied by a discontinuation or decrease of anti-hyperglycemic or lipid-lowering therapies.

By contrast, patients with partial forms of lipodystrophy have a more varied, attenuated, and confounded response. There may be a subset of patients with partial lipodystrophy with very low leptin concentrations and significant metabolic disease that responds to metreleptin, although confounders and missing data present challenges that may be very difficult to overcome in a trial that lacks a comparator.

It is important to ensure that the appropriate patient population is targeted, given the serious risks that may be associated with the drug. Lymphoma and immunogenicity are risks that have been identified at this time; however, given the potential effects of leptin on a variety of organs and cellular functions, the potential for additional risks is theoretically possible.

With respect to lymphoma, although patients with acquired forms of lipodystrophy may be predisposed to developing lymphoma, it is biologically plausible that metreleptin could act as a cancer promoter. It is unknown whether metreleptin had any role in the development of T-cell lymphoma in the three patients with lymphoma in the NIH trial; however, it is also unclear if there is any way to mitigate this risk, given that one of the three patients had no identified risk factors, aside from AGL.

While the primary risk of neutralizing antibodies in the lipodystrophy population is lack of efficacy, the risk of developing a congenital leptin deficiency-like syndrome in non-leptin-deficient populations (which may include some forms of partial lipodystrophy) is significant. Three patients from an obesity program have been identified as having developed neutralizing antibodies in association with low leptin concentrations and excessive body weight increases. Given the interest in obesity therapies, ensuring that only patients who have been clearly identified as benefiting from metreleptin have access to the drug should be the goal of a risk evaluation and mitigation strategy (REMS) if approved. In the post-marketing setting, monitoring patients for the development of neutralizing antibodies, in addition to monitoring for benefit, could be considered as potential strategies to improve the benefit-to-risk relationship.

CLINICAL REVIEW

Application Type	BLA
Application Number	125390
Priority or Standard	Priority
Submit Dates	15 Dec 2010, 2 Apr 2012, 27 Mar 2013 (rolling)
Received Dates	same
PDUFA Goal Date	24 February 2014
Division / Office	DMEP / ODE2
Reviewer Name	Julie K. Golden, M.D.
Review Completion Date	15 November 2013
Established Name	Metreleptin
Proposed Trade Name	Myalept
Therapeutic Class	Recombinant leptin analog
Applicant	Amylin Pharmaceuticals, LLC (Bristol-Myers Squibb Company)
Formulation	Injectable (when lyophilized cake reconstituted in BWFI)
Dosing Regimen	Once daily
Indication	Treatment of metabolic disorders associated with lipodystrophy
Intended Population	Pediatric and adult patients with inherited or acquired lipodystrophy (not HIV-related)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

This section is deferred pending discussion at the Endocrinology and Metabolic Drugs Advisory Committee meeting.

2 Introduction and Regulatory Background

Lipodystrophy

Lipodystrophy is a group of very rare disorders that is characterized by generalized or partial loss of adipose tissue. A recent review[1] estimates 1350 cases of lipodystrophy have been reported worldwide (approximately 1000 patients with inherited forms of lipodystrophy and 350 patients with acquired forms excluding human immunodeficiency virus (HIV)-related lipodystrophy). Based on an assumption that only one fourth of patients are reported, the prevalence of genetic forms of lipodystrophy in the general population has been estimated at less than one in a million. In patients with lipodystrophy, the profound deficiency of adipose tissue leads to accumulation of fat in the bloodstream and ectopic deposition of fat in non-adipose tissues such as liver and muscle, which results in hypertriglyceridemia and insulin resistance. The extent of fat loss often correlates with the severity of the metabolic complications;[1] some patients with lipodystrophy have associated co-morbidities such as diabetes mellitus, pancreatitis, and hepatic steatosis,[2] whereas other patients may have less severe metabolic complications, but significant aesthetic concerns.[3] Many patients require multiple medications to manage their diabetes and/or hypertriglyceridemia.

Lipodystrophy is generally classified as congenital/familial or acquired, and generalized or partial. Therefore, lipodystrophy subtypes will often be referred to in this review as congenital generalized lipodystrophy (CGL), acquired generalized lipodystrophy (AGL), familial partial lipodystrophy (FPL), and acquired partial lipodystrophy (APL). However, within subtypes there may be differences in clinical presentation, and given the ongoing understanding of the underlying genetic basis of disease or progression of fat loss over time, a particular patient's classification may change in the future. Nevertheless, it serves as a useful guide to assessing the risks and benefits of potential therapies, such as metreleptin. Note that HIV-associated lipodystrophy (a form of acquired partial lipodystrophy) is beyond the scope of this review, as patients with this condition were not studied in this development program.

The various subtypes of lipodystrophy have been reviewed; the following is summarized from references 1 and 2:

- Congenital generalized lipodystrophy (CGL) is also known as the Berardinelli-Seip syndrome. CGL is characterized by a nearly complete absence of adipose tissue

and a generalized muscular appearance recognized easily at birth. Severe hyperinsulinemia and hypertriglyceridemia may be present, even during infancy. Extreme hypertriglyceridemia may result in recurrent acute pancreatitis. Patients present with accelerated linear growth, an advanced bone age, and a voracious appetite in early childhood. Over time, patients develop diabetes mellitus and hepatomegaly. Nonalcoholic steatohepatitis may ultimately lead to cirrhosis. After puberty, clitoromegaly and the polycystic ovary syndrome may develop in girls. Only a few affected women have had successful pregnancies[*], whereas affected men have normal fertility. Known genes associated with CGL and the described phenotypes are listed below[†]:

Table 1. CGL Subtypes

Subtype (gene)	Key clinical features	Molecular basis
CGL1 (*AGPAT2*)	Lack of metabolically active adipose tissue since birth	AGPATs are key enzymes required for triglyceride and phospholipid biosynthesis. AGPATs acylate lysophosphatidic acid to form phosphatidic acid. AGPAT2 is highly expressed in adipose tissue.
CGL2 (*BSCL2*)	Lack of both metabolically active and mechanical adipose tissue since birth, mild mental retardation, cardiomyopathy	*BSCL2* encodes seipin, which may play a role in fusion of small lipid droplets and in adipocyte differentiation.
CGL3 (*CAV1*)	Single patient with extreme loss of body fat, short stature, and vitamin D resistance	Caveolin 1 is an integral component of caveolae, present in abundance on adipocyte membranes. Caveolin 1 binds fatty acids and translocates them to lipid droplets.
CGL4 (*PTRF*)	Extreme lack of body fat, congenital myopathy, pyloric stenosis, and cardiomyopathy	PTRF (also known as cavin) is involved in biogenesis of caveolae and regulates expression of caveolins 1 and 3.

Source: Reference 1

- The fat loss with AGL occurs during childhood and adolescence and particularly affects the face, arm, and legs. Subcutaneous fat may also be lost from the palms and soles, while retro-orbital and bone marrow fat may be preserved. The degree of loss of intra-abdominal fat varies. Affected children may have a voracious appetite. Acanthosis nigricans and hepatic steatosis also develop in most patients beginning in childhood. AGL patients often develop hepatic fibrosis, diabetes, and hypertriglyceridemia. The pathogenesis of fat loss in patients with AGL is variable. AGL can be associated with panniculitis (25%), autoimmune diseases such as juvenile dermatomyositis (25%), and in addition, an idiopathic variety has been described (50%). Patients with panniculitis present with adipose tissue infiltrated with histiocytes, lymphocytes, and multinucleated giant cells, together with a granulomatous reaction. These lesions progress from localized loss of

[*] Note that 3 out of 4 pregnancies reported in the metreleptin lipodystrophy development program occurred in women who had a CGL diagnosis
[†] Note that genotype information for the patients in the lipodystrophy trials that support the BLA was not provided to FDA.

subcutaneous fat to loss of fat from almost all subcutaneous regions, eventually causing generalized lipodystrophy.

- Familial partial lipodystrophies (FPL) are heterogeneous, autosomal dominant disorders with several distinct phenotypes (see the table below). The most prevalent is the Dunnigan variety, which is associated with mutations in the lamin A/C gene (*LMNA*).[4] The distribution of body fat is normal during childhood, but with puberty, subcutaneous fat gradually disappears from the arms and legs, resulting in a muscular appearance. Variable and progressive loss of fat from the anterior abdomen and chest occurs later. Many patients, particularly women, gain fat in the face, neck, and intraabdominal region, resulting in a cushingoid appearance. Acanthosis nigricans and the polycystic ovary syndrome are relatively uncommon. The diagnosis is reported to be relatively easy to make in women, but is difficult in men, since many normal men have a muscular habitus. Whole-body magnetic resonance imaging reveals subcutaneous fat loss but increased intermuscular fat in the arms and legs and excess intraabdominal fat. Diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, and atherosclerotic vascular disease are more prevalent in female patients than in male patients. Diabetes usually develops after the second decade of life, associated with multiparity and excess fat in nonlipodystrophic regions in affected women. Marked hypertriglyceridemia has been associated with acute pancreatitis. Although fatty liver occasionally develops, cirrhosis has not yet been reported in these patients.

Table 2. FPL Subtypes

Subtype (gene)	**Key clinical features**	**Molecular basis**
FPLD1, Kobberling (unknown)	Loss of subcutaneous (sc) fat from the extremities	Phenotype not well characterized.
FPLD2, Dunnigan (*LMNA*)	Loss of sc fat from the extremities and trunk (sparing the face and neck) at puberty	Lamins A and C are nuclear lamina proteins and specific mutations may disrupt nuclear function resulting in premature death of adipocytes.
FPLD3 *(PPARG)*	Loss of sc fat from the extremities, especially from distal regions	PPARγ is a critical transcription factor required for adipogenesis. Dominant negative PPARγ mutations may inhibit adipocyte differentiation.
FPLD4 (*AKT2*)	Single family reported with loss of sc fat from the extremities	AKT2, also known as protein kinase B, is involved in adipocyte differentiation and downstream insulin receptor signaling.
FPLD5 (*PLIN1*)	Loss of sc fat from the extremities with small adipocytes and increased fibrosis of adipose tissue	Perilipin 1 is an integral component of lipid droplet membranes and is essential for lipid storage and hormone regulated lipolysis.
Unnamed FPL subtype (*CIDEC)*	Single patient with loss of sc fat from limbs, multilocular, small lipid droplets in adipocytes	CIDEC is a lipid droplet associated protein that inhibits lipolysis and promotes formation of unilocular lipid droplet in adipocytes.

Source: Reference 1

- APL not associated with HIV infection is known as the Barraquer-Simons syndrome. The fat loss occurs during childhood or adolescence, affecting the face, neck, arms, thorax, and upper abdomen in a cephalocaudal fashion. Excess fat may be

deposited in hips and legs. Insulin resistance is infrequent.‡ Patients have low levels of serum C3 accompanied by detectable levels of C3 nephritic factor. C3 nephritic factor–induced lysis of adipocytes may be involved in the pathogenesis of this form of lipodystrophy. It is also associated with other autoimmune conditions. Membranoproliferative glomerulonephritis has been reported in approximately 20 percent of patients.

Leptin (Reviewed in Reference 5)

Leptin in humans and other mammalian species is the protein product of the *ob* gene. Leptin is a 146-amino acid protein synthesized primarily in white adipose tissue, and is homologous in structure to a cytokine. Secreted leptin acts on hypothalamic feeding centers in the brain, signaling the energy stores of the body (e.g., low fat stores in starvation decrease circulating leptin, leading to an increase of energy intake).

Circulating leptin concentrations strongly correlate with body fat stores. In one paper, mean serum leptin concentrations in 139 obese individuals was 31.3 ± 24.1 ng/mL, as compared with 7.5 ± 9.3 ng/mL in 136 normal-weight individuals ($p < 0.001$).[6] Leptin concentrations are greater in females compared to males, and some authors have found this to be true even when correcting for differences in body composition,[7,8] while others have not.[6] The third National Health and Nutrition Examination Survey conducted in 6303 women and men aged 20 years or older reported the mean serum leptin concentration in women to be 12.7 ng/mL and in men 4.6 ng/mL.[9] (See the table from this publication below, which provides leptin concentrations by sex and race/ethnicity.) Leptin concentrations fall and rise, respectively, with short-term fasting and refeeding,[10] although leptin does not appear to rise acutely after individual meals.[11]

Table 3. Range of Leptin Concentrations in Adults

Serum leptin concentrations in non-Hispanic white, non-Hispanic black, and Mexican American women and men aged ≥20 y: United States, 1988–1994

Sex and ethnicity	Geometric $\bar{x} \pm$ SEM	Percentile[1]								
		5th	10th	15th	25th	50th	75th	85th	90th	95th
		μg/L								
Women										
All ethnicities ($n = 3366$)[2]	12.7 ± 0.37	3.3	4.6	5.6	7.7	13.2	21.8	28.0	32.3	40.4
Non-Hispanic white ($n = 1441$)	12.2 ± 0.41	3.3	4.4	5.4	7.3	12.3	20.9	27.7	32.0	39.7
Non-Hispanic black ($n = 957$)	16.4 ± 0.55[3]	4.3	6.2	7.8	10.4	17.7	26.7	33.8	39.7	46.2
Mexican American ($n = 823$)	14.3 ± 0.57	4.5	6.1	7.3	9.6	15.4	21.9	26.7	30.3	36.2
Men										
All ethnicities ($n = 2937$)[2]	4.6 ± 0.12	1.4	1.7	2.0	2.7	4.4	7.4	9.9	11.7	15.6
Non-Hispanic white ($n = 1225$)	4.7 ± 0.14	1.4	1.8	2.2	2.7	4.5	7.4	10.0	12.0	15.8
Non-Hispanic black ($n = 768$)	4.1 ± 0.17[4]	1.2	1.5	1.7	2.2	4.0	7.3	9.2	11.6	15.8
Mexican American ($n = 828$)	4.4 ± 0.14[4]	1.5	1.9	2.1	2.7	4.2	6.9	8.7	10.6	13.4

[1] Untransformed leptin concentration.
[2] Includes data for ethnicities not shown as separate categories.
[3,4] Significantly different from non-Hispanic whites: [3] $P < 0.05$, [4] $P < 0.01$.

Source: Reference 9

‡ This may explain why there are few patients with APL in the metreleptin program.

Leptin receptors are members of the class I cytokine receptor family and have multiple isoforms, with identical extracellular ligand binding domains and varying lengths of intracellular domains for signal transduction.[12] In addition to its effects on energy homeostasis, leptin and its receptors appear to serve an important role in inflammation, via activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway,[13] and reproduction.[14]

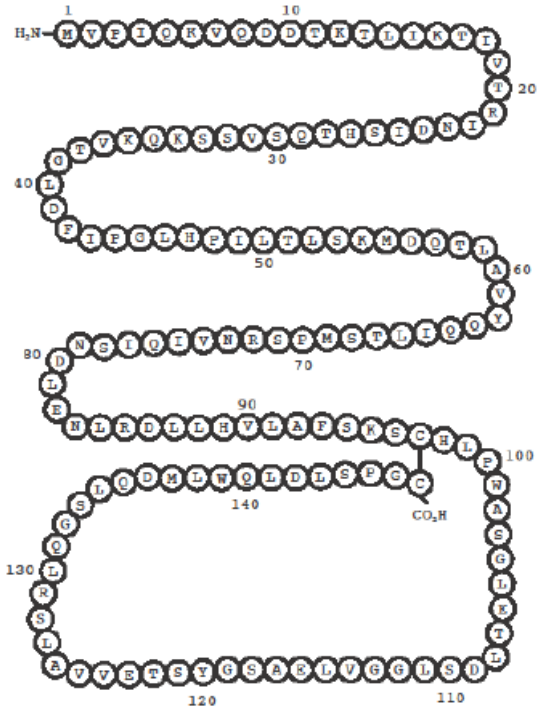
2.1 Product Information

The new molecular entity (NME), metreleptin, is a recombinant analog of the endogenous human hormone, leptin. The proposed tradename is Myalept.

Metreleptin is a 147 amino acid, non-glycosylated polypeptide with one disulfide bond. It has the empirical formula $C_{714}H_{1167}N_{191}O_{221}S_6$ and a molecular weight of approximately 16.2 kDa. Metreleptin differs from the human leptin sequence by one additional amino acid, methionine, located at the amino-terminal end.

The amino acid sequence and structure for metreleptin is shown in the following figure.

Figure 1. Metreleptin Structure



Source: BLA 125390 3.2.S.1.2, Figure 1

The proposed indication is as follows:[§]

MYALEPT (metreleptin for injection) is a recombinant analog of human leptin indicated for the treatment of pediatric and adult patients with:

- *Generalized lipodystrophy.*
- *Metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis.*

2.2 Currently Available Treatments for Proposed Indications

There are no approved drugs specifically for the treatment of metabolic disorders associated with lipodystrophy. Currently available treatments for this orphan population are directed toward addressing the individual metabolic abnormalities, and can include insulin and oral hypoglycemic agents for insulin resistance and diabetes, and statins, fibrates, niacin, and fish oil for hypertriglyceridemia. Decreasing caloric intake can also improve metabolic disorders associated with lipodystrophy.

2.3 Availability of Proposed Active Ingredient in the United States

Metreleptin is only available as an investigational medication in the U.S.

2.4 Important Safety Issues with Consideration to Related Drugs

Not applicable. There are no other related drugs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following table summarizes the metreleptin regulatory history. Metreleptin has been studied for treating lipodystrophy-related conditions since 2000.

Table 4. Metreleptin Regulatory History

Date	Activity
16 May 2001	Amgen EOP2 meeting with the Agency (IND 50259) • The Division agreed that study 991265 (8-month initial trial in 9 patients) was sufficient to use as the single pivotal trial in a leptin NDA • The Division suggested that the NDA could be strengthened by following patients during a drug withdrawal and re-treatment period • Concern about off-label use was raised; there was discussion about whether this could be addressed through restricted distribution • The sponsor noted that dose and schedule were developed to achieve replacement levels of leptin, but that triglyceride (TG) and glucose levels, rather than leptin levels, were used to

[§] Revised 5 Nov 2013

Date	Activity
	titrate the drug • The Division indicated that dosing rationale should be included in the NDA • The Division agreed that sufficient data exist from studies 991265 and 970161 [study in primary leptin deficiency] to support use in pediatric patients • The Division concurred that the safety package consisting of the obesity and diabetes trials conducted with metreleptin would provide sufficient safety data to support the NDA, and that these data could be submitted as an ISS without individual study reports • The Division stated that the indication should identify the disease population and benefits expected with the drug • FDA could not state what the review status (i.e., priority vs. standard) would be at this time • The preclinical program is adequate for the narrow indication/population
22 Aug 2001	Amgen was granted orphan designation of metreleptin for the treatment of metabolic disorders secondary to lipodystrophy (OD 01-1467)
22 Oct 2001	Amgen was granted fast track designation of metreleptin for the treatment of metabolic disorders associated with lipodystrophy
03 Mar 2006	Amylin assumed sponsorship of metreleptin (IND 50259) from Amgen Amylin assumed ownership of Amgen's metreleptin inventory manufactured at 2 sites (Thousand Oaks and Lake Centre) and Amgen's master and working cell banks
17 Oct 2007	Type C meeting convened to confirm Amylin's interpretation of Amgen's EOP2 meeting in 2001 and to obtain DMEP's guidance related to updated clinical and nonclinical data for lipodystrophy • Clinical package of 29 patients from NIH trials sufficient • Non-clinical package sufficient • HIV-related lipodystrophy not within the scope of the proposed indication
01 May 2008	CMC IND amendment filed to add Sandoz GmbH (Kundl, Austria) as an additional manufacturer of drug substance
19 May 2008	Treatment IND 101824 filed as means to expand access to metreleptin for patients with metabolic disorders associated with lipodystrophy until submission of the NDA Sandoz GmbH is proposed as an additional drug substance manufacturer for the treatment IND
05 Jun 2008	Teleconference with FDA to discuss using Sandoz drug substance in the treatment IND
08 Jun 2008	FDA authorized the "Treatment IND May Proceed", but only using Amgen drug substance for clinical use FDA indicated that additional work needed to be performed in order to establish comparability between Sandoz and Amgen drug substance, including a 28-day bridging toxicology study
Feb 2009	FDA was notified about 2 cases of peripheral T cell lymphoma that occurred in the lipodystrophy program (IND 60534); in response, Amylin: • Amended the exclusion criteria of the treatment protocol FHA101 (IND 101824) to exclude those patients with acquired lipodystrophy who have clinically significant hematologic abnormalities, such as neutropenia and/or lymphadenopathy • Notified all investigators and physicians who are involved in lipodystrophy clinical trials and compassionate use treatments with metreleptin of these reports of peripheral T-cell lymphoma and assessment of these cases
10 Sep	Amylin provided additional CMC and nonclinical information on metreleptin to qualify Sandoz GmbH as a drug substance manufacturer and to seek agreement that Sandoz drug substance is

Date	Activity
2009	suitable for clinical use
22 Oct 2009	Request for comments: Amylin proposed filing the lipodystrophy NDA with Amgen drug substance because of its long history of clinical use without apparent safety concerns and continuing stability and based on the large quantity of Amgen drug substance available to supply metreleptin for this small orphan population for the foreseeable future
10 Dec 2009	FDA response indicating lack of concurrence that comparability had been fully established between Amgen and Sandoz metreleptin material by the CMC characterization information provided. FDA recommended against an NDA filing with Amgen drug substance, despite its use to supply the ongoing treatment protocol in lipodystrophy. The lack of a site for pre-approval inspection categorized the Amgen drug substance as out of compliance with Agency policy.
08 Feb 2010	Amgen communicated an intention to file the metreleptin for lipodystrophy NDA with Sandoz material To expedite availability of this orphan designated drug, Amylin submits "Request for Submission of Portions of an Application" (i.e., rolling review)
02 Apr 2010	Amylin requested a teleconference with the chemistry reviewer to clarify the scope of the Agency's information requests to facilitate transparency and ensure submission of the appropriate information and data
09 Apr 2010	Agency issued advice/information request for a briefing book and meeting to discuss the development proposal and the following specific issues: • Amylin's plans for sourcing drug substance and drug product • Possible alternative scenarios if drug substance from the proposed new drug manufacturer, Sandoz GmbH, cannot be qualified as comparable to material manufactured by Amgen • The need for additional clinical and nonclinical information if the Sandoz material is not comparable • Amylin's plans for use of Amgen material and Sandoz drug substance within a single NDA • Details on the status and projected timeline for each portion of the lipodystrophy NDA
30 Jul 2010	Agency's acceptance of rolling submission timeline and plans
13 Oct 2010	Letter states that per the Patient Protection and Affordable Care Act the Agency now believed that the appropriate marketing application for metreleptin is a BLA
18 Oct 2010	Agency's acceptance of chemical comparability of the Sandoz material
22 Oct 2010	Amylin submitted a request for Agency's comments regarding Amylin's proposed filing strategy for the CMC portion of the rolling BLA submission, a strategy that would allow compliance with the agreed upon rolling submission schedule
16 Nov 2010	Results of the 1-month toxicology study in mice adequately bridge the Sandoz-sourced metreleptin to the non-clinical data available for the Amgen sourced metreleptin. The non-clinical data support initiation of clinical studies with the Sandoz-sourced metreleptin. Amylin was asked by FDA to collect anti-leptin antibody data on patients transitioned to as well as those naïve to Sandoz metreleptin and include that information in the BLA safety update.
15 Dec 2010	Clinical and non-clinical modules submitted along with draft product label Clinical module included: NIH trials: N=55 patients; FHA101 trial: N=10 patients
03 Feb 2011	Agency requested an assessment of comparability between the Sandoz 2000 L DS and Sandoz 1000 L materials
May 2011	Meeting with Amylin to discuss 2 patients in the obesity program (IND 50259) with neutralizing antibodies to leptin and excessive weight gain
01 Apr	Submission of Module 3 including data to establish comparability between Sandoz DS made at

Date	Activity
2012	2 different fermentation scales. The submission also included: • Clinical Addendum to provide clinical experience with Sandoz DS focusing on Amylin's assessment of the immunogenicity of metreleptin manufactured at Sandoz in comparison with metreleptin manufactured at Amgen • Proposed RMP • Updated draft labeling
30 May 2012	Discuss the completeness of the BLA As studies were still ongoing and enrolling patients, the Agency conveyed that there were additional evaluable data from patients who had enrolled in these studies after the datacuts of the original Dec 2010 submission and that such data should be included in the BLA at the time of filing
June 2012	Amylin submitted non-clinical and CMC information amendments to IND 101824, in order to begin dosing patients using metreleptin manufactured at Sandoz at the 1000L scale
11 Jul 2012	Amylin and Agency had a teleconference to agree on the information/data to complete the BLA • Agency specifically requested additional efficacy and safety analyses as well as a comprehensive assessment of immunogenicity (lipodystrophy and obesity)
22 Jul 2012	FDA requested additional analyses and specific format for data presentation for Summary of Clinical Safety update, Summary of Clinical Efficacy update, and Clinical Addendum
Aug 2012	FDA informed of a 3rd patient in the obesity program (IND 50259) with neutralizing Abs to leptin and excessive weight gain
23 Oct 2012	Agency recommended Amylin request a pre-BLA meeting prior to submission as outlined under PDUFA V's "The Program"
30 Nov 2012	The Agency received an email from Amylin indicating there may be a possible shortage of metreleptin due to delays in manufacturing of drug product and a shortage of bacteriostatic water for injection (BWFI)
05 Dec 2012	Type A meeting: Discussed the manufacture and clinical use of metreleptin for lipodystrophy Because of possible drug shortage, the company contacted investigators and asked them to stop enrolling any new patients
17 Dec 2012	Pre-BLA meeting: • Agreements confirmed with regard to outstanding clinical documents/data to complete the BLA filing (NIH trials N = 72; FHA101 trial N=28) • Non-clinical information was also confirmed • RMP adequate to mitigate for risks now • A potential exists for a REMS request during review as noted in the preliminary response from FDA • Clarification was received for the 2013 manufacturing campaign
2 Jan 2013	The Agency requested additional information to be submitted with the final section of the BLA in order to facilitate the OSI development of clinical investigator and sponsor/monitor/contract research organization inspection assignments
Jan 2013	FDA informed of 3rd patient in the lipodystrophy program (IND 60534; NIH trials) diagnosed with lymphoma
22 Jan 2013	FDA requested lymphoma case analysis and update to Investigator's Brochure and all informed consent forms to include available information about lymphoma in metreleptin-treated patients
29 Jan 2013	FDA provided advice on performing in-process intermediate hold time study
1 Feb 2013	Agency requested a status update on obtaining BWFI for use with metreleptin

Date	Activity
26 Feb 2013	Amylin submitted a response stating that they do not anticipate any shortage of BWFI as the supply has been secured for the duration of 2013
27 Feb 2013	FDA requested breakdown of clinical data from 11 Jul 2011 / 07 Mar 2012 cutoffs (N=100) and Jan 2013 cutoff (N = 125, 4-month safety update) by sex and lipodystrophy subtypes [for oncology consultant] FDA requested estimated date for submission of the last BLA module
27 Mar 2013	BLA submitted • Updated labeling • Updated risk management plan • CMC data • Updated clinical data

Source: BLA 125390, Section 2.5 Clinical Overview Appendix 3, date 27 Mar 2013; internal FDA files

2.6 Other Relevant Background Information

Metreleptin received marketing approval in Japan on 25 Mar 2013 for treatment of lipodystrophy.[15]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There is no evidence to suggest that the investigators who were involved in treating patients with metreleptin, nor the sponsor, conducted the trials and the analyses with anything but good intent. Nevertheless, there are a number of limitations to these trials that call into question the validity of some results. Furthermore, given the nature of the disease (rare, with heterogeneous presentation), the development program (evolving over time, open-label), and the regulatory program under which this was submitted (fast track, utilizing a rolling review[16]), the application was very challenging to review.

This BLA was submitted over time in "chunks", as additional data cuts were conducted of ongoing data. Unfortunately, some of the data from earlier data cuts were not available for later data cuts, and finding earlier data was challenging, since it could have been included in various documents from a variety of submission dates. In addition, earlier data did not reflect later data as the population enrolled changed over time; therefore how representative these data analyses are, is unclear.

Some of the efficacy challenges and limitations, and questions surrounding efficacy that arose from the review, are as follows:

- Although the endpoints were pre-specified, the investigators used considerable flexibility in enrolling potential patients. It was unclear in some cases what metabolic disorder they were in fact treating, and therefore, what endpoints were relevant.

- There was no placebo, and in many forms of lipodystrophy the natural history is not clearly defined (this is a heterogeneous group of diseases). Therefore, how do we assess the treatment effect?

  - For most patients there was not a narrative of the course of disease prior to study enrollment. In some patients where that information is available, the metabolic disease appeared to wax and wane (particularly hypertriglyceridemia).

- What are the characteristics of patients who are not responding? (and how is "responder" defined?) Without comprehensive and systematic compliance data, it is difficult to attribute poor metreleptin response to poor compliance.

- Dietary intake, a critical part of lipodystrophy management, was not reported; therefore, it is unknown what dietary changes patients made once enrolling in the trial.

- Background medications are significant confounders:

  - Medication changes, including increases or additions of relevant concomitant medications, were made in the first year, prior to the endpoint of interest

  - Background medication compliance was inconsistently recorded

  - It was not clear why some patients were not optimally treated for their metabolic disease(s) prior to enrollment

  - Metreleptin compliance likely covaries with dietary and background medication compliance

- It was not clear what was happening between visits in terms of compliance, diet, medications, laboratory data, illnesses, etc.

- There were a number of data issues from that impacted the confidence in the results:

  - missing data

  - alternative / adjusted baseline visits

  - patient data or information in the BLA was different than that presented in key publications

  - protocol deviations (e.g., NIH Patient 90165 was enrolled without meeting inclusion criteria for metabolic abnormalities; NIH Patient 90146 was enrolled with a baseline leptin concentration that exceeded 12 ng/mL; some patients were started on new medications or had medication doses increased early in the trial)

  - there were several key protocol changes over time

  - secondary efficacy endpoint data from the NIH were not available after the first data cut

  - some patients with elevated hemoglobin (Hb) A1c were not reported as having diabetes mellitus at baseline (therefore calling into question medical history data)

- Some patients were related (e.g., sisters, cousins)[17] and this information was not reported; this could impact the generalizability of the findings

- No formal dose evaluation was conducted

Safety assessment challenges and limitations included:

- Problems in adverse event / disposition reporting, e.g.:

  - Some adverse events were not reported for years (e.g., one case of T-cell lymphoma, one case of breast cancer)

  - Certain discontinuations should have been counted as adverse events rather than “other” or “ineligible to continue”

  - Probably impossible to capture all adverse events, particularly in patients who are only coming into the NIH yearly; in some cases the investigators were informed about hospitalizations months or years later

  - Five patients were reported in the database to have discontinued due to non-compliance, although only four were reported in the Clinical Safety Update report; the one patient (90102) not captured may have had an contributing adverse event that was not reported (worsening renal function)

- Problems with documentation, e.g.:

  - Numerous changes were made to the case report forms, in some cases years later (for example, hand written changes were made to severity, seriousness, or relatedness of an adverse event)

  - Data were entered into case report forms electronically well after the visit, in some cases years later

  - No hospitalization records for cases of pancreatitis were provided in cases where the PI determined the event occurred due to a sudden discontinuation of metreleptin

  - Puberty data were not collected on a case report form and errors were found in the summary tables

- Problems with adverse event / disposition coding, e.g.:

  - A suicide attempt was miscoded as suicidal ideation

  - A patient who was thought to have discontinued due to an adverse event (proteinuria) was later determined to have been transferred to another program in another country

3.2 Compliance with Good Clinical Practices

This section is deferred pending FDA inspection reports.

3.3 Financial Disclosures

For NIH-sponsored trials 991265 and 20010769, NIH has confirmed that their investigators do not have any reportable conflicts of interests.

Financial disclosure information was provided for the sponsor-initiated FHA101 trial in patients with lipodystrophy and the five pramlintide-metreleptin trials in patients with obesity referenced in the Clinical Addendum **(**DFA101, DFA102, DFA102E, DFA104, and DFA106). For clinical investigators identified as having disclosable financial interests, specific details including the size and nature of the financial interest were provided as an attachment to Form FDA 3455.

- In FHA101 (total N=28), no investigators (out of three) and no sub-investigators disclosed financial interests

- In (b) (4) (total N= (b) (4)), one investigator ((b) (4) and two sub-investigators disclosed financial interests

  - A sub-investigator who enrolled (b) (4) patients is a member of the advisory board for the Amylin/Speakers Bureau exceeding $25,000

  - An investigator who enrolled [redacted] patients owned [redacted] shares of Amylin stock
  - A sub-investigator who enrolled [redacted] patients received honoraria exceeding $25,000

- In [redacted] (total N [redacted] two investigators (of [redacted] and no sub-investigators disclosed financial interests
  - An investigator who enrolled [redacted] patients received a speaking honorarium exceeding $25,000
  - An investigator who enrolled [redacted] patients owned [redacted] shares of Amylin stock
- In [redacted] (total N= [redacted] enrolled, out of [redacted] patients from [redacted] one investigator (out of [redacted] and no sub-investigators disclosed financial interests
  - An investigator who enrolled [redacted] patients owned [redacted] shares of Amylin stock
- In [redacted] (total N= [redacted] enrolled, N= [redacted] randomized), one investigator (out of [redacted] and one sub-investigator disclosed financial interests
  - A sub-investigator who enrolled [redacted] patients received honoraria / research grant exceeding $25,000
  - An investigator who enrolled [redacted] patients is a member of the advisory board for Amylin exceeding $25,000
- In DFA106 (total N=419 enrolled out of 784 eligible patients), no investigators (out of 36) and no sub-investigators disclosed financial interests

Reviewer comment: In all cases, the impact of the financial disclosures was mitigated by the fact the trials had multiple sites. The conclusions of the trials were based on the overall data, not from any single investigative site.

No financial information was provided for any of the Amgen-sponsored trials. Upon contact from the BLA sponsor and after reviewing their records, Amgen confirmed that financial disclosures for investigators from the Amgen-sponsored obesity program trials were not found. Furthermore, they have noted that prior to 02 Feb 1999, sponsors of clinical trials such as Amgen were under no obligation to collect this additional information per 21 CFR Part 54 for regulation.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This section is deferred pending the completed review of the chemistry, manufacturing, and controls data.

4.2 Clinical Microbiology

This section is deferred pending the completed review of drug product and drug substance microbiology. Metreleptin is not an antimicrobial, therefore clinical microbiology is not applicable.

4.3 Preclinical Pharmacology/Toxicology

This section is deferred pending the completed review of the non-clinical data.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Clinical evaluations of metreleptin on mechanistic endpoints such as free fatty acids and measures of insulin resistance are described in Section 6.1.5. However, these assessments cannot distinguish whether there is an independent effect of metreleptin on insulin signaling, or if it exerts its effect via appetite alone (i.e., decrease in hyperphagia with subsequent decrease in energy intake). Without a placebo-control, understanding the mechanism of action is important in attempting to distinguish how much of the observed effect may be attributed to the drug versus additional benefits of enrolling in a clinical trial and the subsequent impact via dietary compliance (as well as background medication changes).

It is important to note that caloric intake might make a considerable impact on markers of disease. Wolfsdorf, et al. reported in a 1979 abstract on a 23-year-old female with CGL.[18] At baseline, her *ad libitum* caloric intake was reportedly 2500 kcal/d. Baseline triglyceride (TG) value was 1350 mg/dL, glucose was 137 mg/dL, insulin was 60 µU/mL, and she had hepatomegaly. By report, the patient was placed on a 48-hour fast, then her dietary intake was reduced to 1900 kcal/d for 18 days. At the end of the treatment period, her TG was 80 mg/dL, glucose 77 mg/dL, insulin 8.5 µU/mL, and hepatomegaly was reportedly no longer present. The authors stated, “The reported efficacy of various drugs may reflect their anorectic action and should be compared to the effects of caloric reduction alone.”

Furthermore, although energy intake and appetite data were not provided in the BLA, it is reported in the literature[19] that the NIH lipodystrophy patients (at least those reported in this particular publication) decreased energy intake by 45% with metreleptin treatment.

In the BLA there is a report of a patient (90101, a 17-year-old female with AGL) who underwent a controlled withdrawal of metreleptin (see description in Section 6.1.4). Despite reported clamping of caloric intake, her metabolic parameters worsened over several days, supporting the concept of an effect of metreleptin independent of the dietary effects. This is consistent with the effects of metreleptin in paired feeding experiments in animal models of lipodystrophy.[20] However, this was a very severely-affected patient who required weekly plasma exchange therapy due to severe medication-resistant hypertriglyceridemia,[21] and in addition is only a single case, which would therefore require further verification.

4.4.2 Pharmacodynamics

Formal pharmacodynamic assessments were not conducted. See Section 6 for efficacy assessments.

4.4.3 Pharmacokinetics

Mean serum fasting leptin concentrations over the intial two years of metreleptin treatment in an earlier data cut of patients from the NIH trials (N = 55) are presented in the table below; note that considerable variability (minimum and maximum) was seen.

Table 5. Fasting Concentrations of Serum Leptin, NIH Trials 2009 Datacut (N = 55)

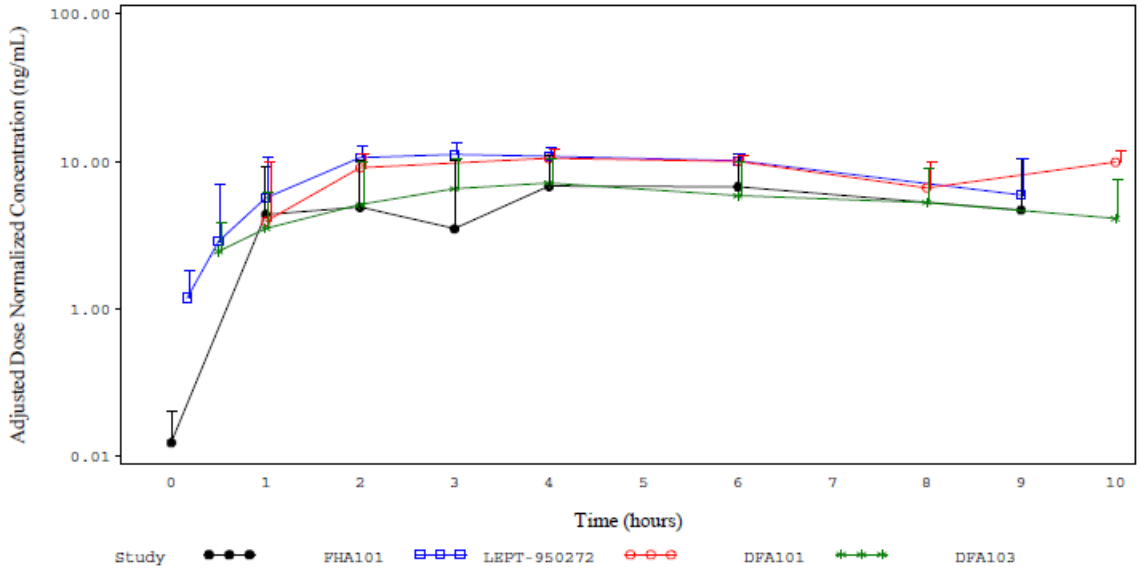
		Baseline	Visit			
	Statistics	Baseline [1]	Month 4	Month 8	Month 12	Year 2
Fasting Leptin (ng/mL)	n	51	34	34	34	19
	Mean (SE) [2]	2.8 (0.39)	18.6 (2.7)	30.0 (4.1)	29.9 (4.7)	24.5 (5.6)
	Min, Max	0.3, 14.1	1.1, 62.2	1.86, 82.6	2.2, 96.9	1.7, 82.1

SAP = statistical analysis plan; SD = standard deviation; SE = standard error.
[1] In general, baseline measurements were defined as the last as the last available value before the subject received the first injection of metreleptin. See SAP for details.
[2] Leptin concentrations at baseline are presented in mean (SE).
Notes: Data are shown for the ITT patients for whom leptin concentrations were available at each time point. The time of last metreleptin dose prior to fasting leptin blood sample was not collected.
Source: Summary of Clinical Pharmacology, Table 5

The pharmacokinetic (PK) properties of metreleptin in lipodystrophy patients were assessed in a subset of patients with lipodystrophy from the FHA101 trial [conducted by the sponsor under a treatment IND, see Section 5.3 and Section 9.4 (Appendix)]. The

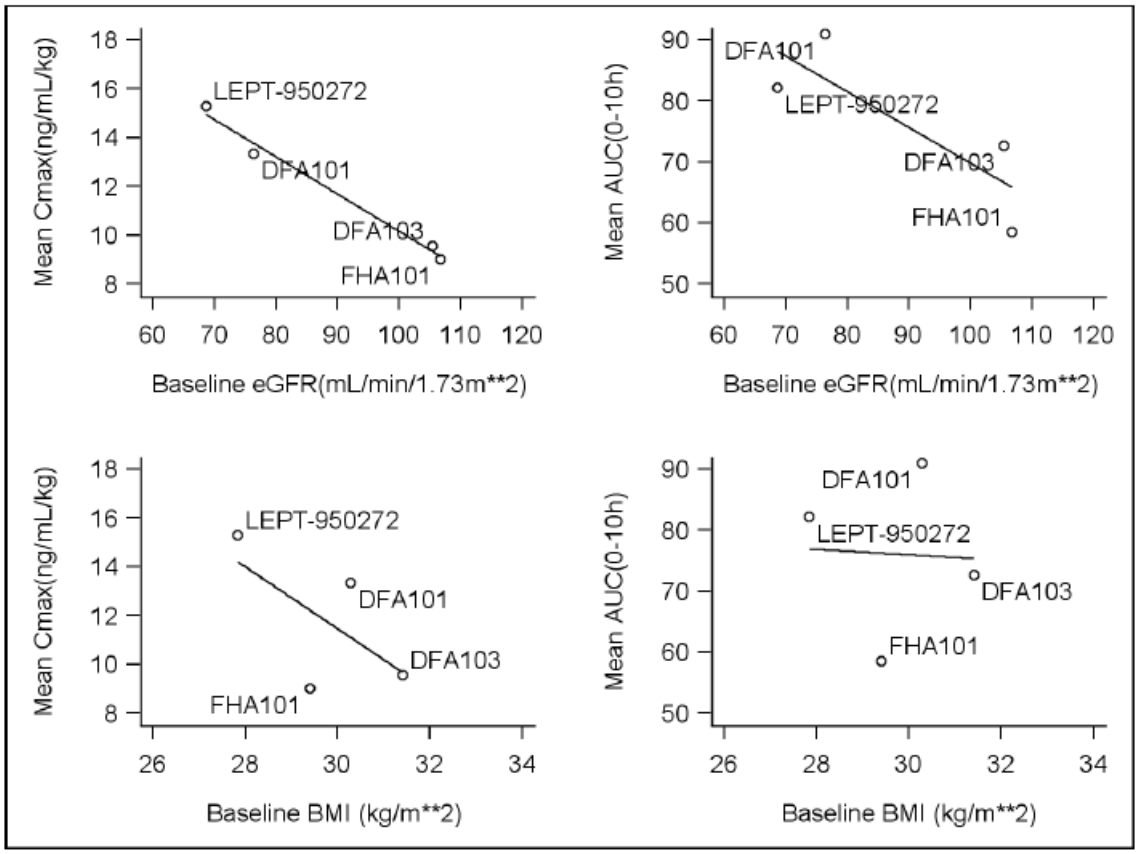
limited number of lipodystrophy patients with PK profiles available for the analyses should be considered when interpreting these results. The PK properties of metreleptin for the subset of patients from FHA101 were then compared to the PK properties of metreleptin in healthy normal weight individuals and overweight and obese patients from the Amgen trial LEPT-950272, and Amylin trials DFA101 and DFA103. The PK properties of metreleptin (C_{max}, $AUC_{0\text{-}10h}$ and T_{max}) were similar between the lipodystrophy patients and healthy individuals after correcting for differences in renal function (with higher estimated GFR in lipodystrophy patients compared to healthy individuals).

Figure 2. Mean (+SD) Metreleptin Pharmacokinetic Profiles (Baseline Adjusted and Dose Normalized) after a Single Dose of Metreleptin, FHA101, LEPT-950272, DFA101, and DFA103 Trials



Source: Technical Report REST120204, Figure 2

Figure 3. Mean Metreleptin Exposure (C_{max} and AUC_{0-10h}) versus Mean eGFR or Baseline BMI, FHA101, LEPT-950272, DFA101, and DFA103 Trials

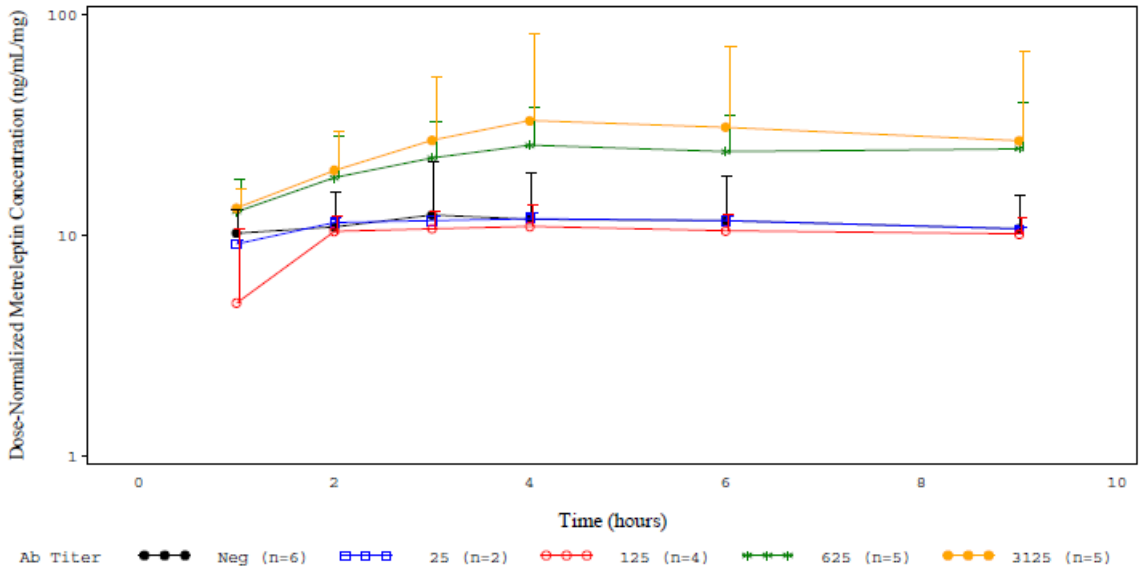


Source: Technical Report REST120204, Figure 3

Exploratory plots of metreleptin exposure over time for FHA101 suggest that higher exposure of metreleptin occurs with higher antibody titers (e.g., 625 and 3125). The effect of antibody titers greater than 3125 could not be assessed due to negative interference in the immunoassay of leptin (including metreleptin) concentrations. Higher plasma exposure of metreleptin with higher antibody titers in lipodystrophy patients is consistent with the observations made in studies of otherwise healthy overweight/obese people.[**]

[**] As reported by the sponsor.

Figure 4. Mean Concentration-Time Profiles of Metreleptin (PK1 and PK2 Combined) Stratified by Antibody Titer (Dose Normalized)



Source: Technical Report REST120204, Figure 5

For FHA101, metreleptin was initially administered as a twice a day (BID) dosing regimen with the option to change from BID to once a day (QD) dosing using the same total daily dose once metabolic parameters had stabilized. The daily exposures of metreleptin for the QD dosing regimen were consistent with the BID dosing regimen when the same total daily dose was administered.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6. Studies Supporting the Metreleptin for Lipodystrophy BLA

Study	Patient Population	Number of Metreleptin-Treated Patients	Position in BLA	Endpoints Supported
NIH Trials 991265/20010769 [1]	Lipodystrophy patients	72 [2]	Pivotal	Safety and efficacy
Treatment IND FHA101 [1]	Lipodystrophy patients	28 [3]	Supporting	Safety and efficacy
Amgen 5-trial ISS (metreleptin monotherapy)	Obese patients without lipodystrophy	784 (vs. 351 placebo)	Supporting	Safety (including immunogenicity)
Other 10 Amgen obesity trials (metreleptin monotherapy)	Obese patients without lipodystrophy	379 [4] (vs. 167 placebo)	Supporting	Immunogenicity
Amylin obesity program (metreleptin/pramlintide combination)	Obese patients without lipodystrophy	615 (vs. 203 placebo)	Supporting	Immunogenicity

NASH=non-alcoholic steatohepatitis; HA=hypothalamic amenorrhea; DM=diabetes mellitus
[1] ongoing trials or ongoing treatment, except investigator-initiated study with C. Levy Marchal as principal investigator
[2] As of 11 July 2011 data cut
[3] As of 7 Mar 2012 data cut
[4] Excludes 4 patients with congenital leptin deficiency treated with metreleptin in Amgen trial 970161

Source: BLA 125390, Section 2.5 Clinical Overview, date 27 Mar 2013; sponsor response to FDA 24 Jun 2013, Table 3

5.2 Review Strategy

I was the primary reviewer for clinical efficacy and safety. I received input from the FDA statistics reviewer and clinical reviewers from the Divisions of Hematology Products, Pulmonary, Allergy, and Rheumatology Products, and Gastrointestinal and Inborn Errors Products.

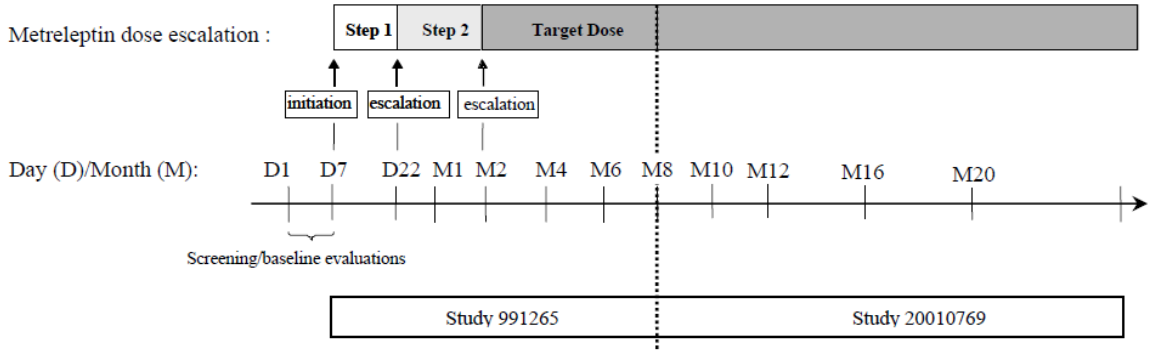
5.3 Discussion of Individual Studies/Clinical Trials

NIH Trials

Trial 991265-20010769 is entitled, *a long-term, open-label study to evaluate the effect of leptin replacement on efficacy and safety in patients with lipodystrophy*. The original protocol (991265) was submitted under IND 60534 in June 2000, with two subsequent protocol amendments. The trial was conducted at the Clinical Centers of the National

Institutes of Health (NIH) and the University of Texas Southwestern in Dallas (UTSW).[††] At that time, metreleptin drug substance was manufactured by Amgen. The eligibility requirements, the program of metreleptin administration, and major endpoints comprised the core protocol that both centers followed. Each center also conducted individual assessments of additional parameters based on their specific research interest and available facilities. The basic visit structure of protocol 991265 is illustrated in the following schematic:

Figure 5. Study Overview and Visit Structure for Patients Enrolled in Study 991265



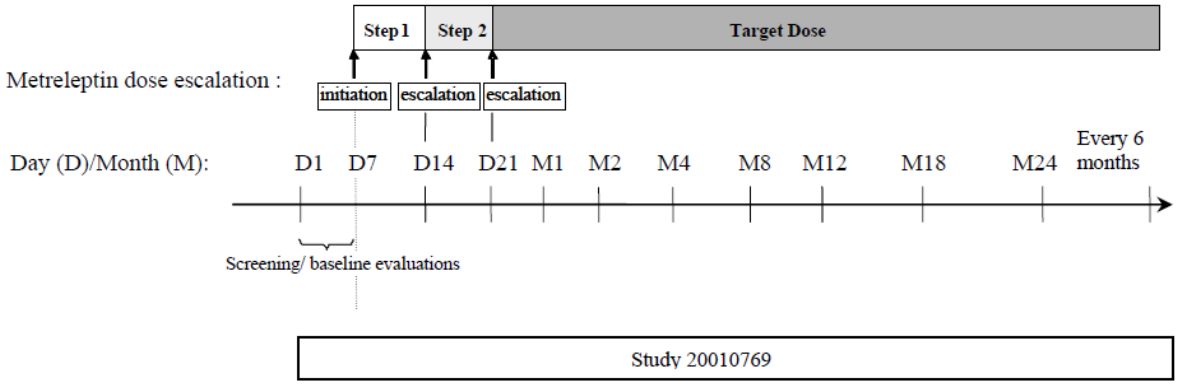
[1] Metreleptin target dose was achieved via a 2-step dose escalation per protocol.
[2] Following the first metreleptin dose on Day 7, patients were observed as inpatients for at least 48 hours. Patients were not required to visit the site on Day 22

Source: Clinical Efficacy Update, Appendix 1

The long-term protocol (20010769) was designed to continue and expand protocol 991265 by (1) lowering the inclusion age criterion from 14 years and older to 5 years and older, (2) evaluating long-term (one-year) efficacy, and (3) including patients with less severe leptin deficiency. The basic visit structure for protocol 20010769 is illustrated in the following schematic:

[††] Note that only the data from the NIH is included in the BLA submission, due to previous agreements with the Agency. Patients 1 and 2 from the UTSW site continued metreleptin treatment under 991265 until January 2003, after which they enrolled in an investigator study under a separate research IND and continued metreleptin treatment. Patient 1 is still on metreleptin treatment, while Patient 2 withdrew in January 2008 due to inconvenience of participation in the study including travel to study site. The third patient at UTSW continued metreleptin treatment under 991265 until June 2002 after which he was lost to follow up, although the investigator indicated that the patient was “alive and well” several years after discontinuation of metreleptin.

Figure 6. Study Overview and Visit Structure for Patients Enrolled in Study 20010769



[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.

Source: Clinical Efficacy Update, Appendix 1

Subsequently five amendments were made to the protocol; key changes included increasing sample size, expanding entry criteria to include patients with progressively less severe leptin-deficiency, lowering age of entry to 6 months, and changing the dosing regimen.[‡‡]

Summaries of Protocols 991265 and 20010769 can be found in Section 9.4 (Appendix) of this review.

[‡‡] Regarding dosing changes, the following comment was noted in Protocol 20010769: *A new Appendix 7 was added to the protocol document (pages 52-53) to layout current proposed dosing in chart form. These proposed doses are based on the observations of 38 patients that we have treated on leptin therapy for 3 months up to 6 years. Doses have needed to be increased from earlier versions, as target levels for glycemia and lipids levels are trying to be achieved. For example in 6 women with partial lipodystrophy, only 2 were able to achieve target levels for glycemia after 1 year, and 1 patient for both glycemia and lipids. But when the dose of leptin was increased to 0.12 mg/kg/day along with maximizing their existing standard therapies, all had HbA1c levels less than 8.0% and 5 out of 6 had HbA1c levels less than 7%. This new chart will assist in dose escalations, and double checking by the pharmacy of leptin therapy ordered.* ***Reviewer comment: It is noted in these patients with partial lipodystrophy that efficacy was achieved when, in addition to increasing the leptin dose, existing standard therapies were maximized. Efficacy of metreleptin is very difficult to assess in such situations where multiple interventions were performed simultaneously. This issue was explored further in Section 6.***

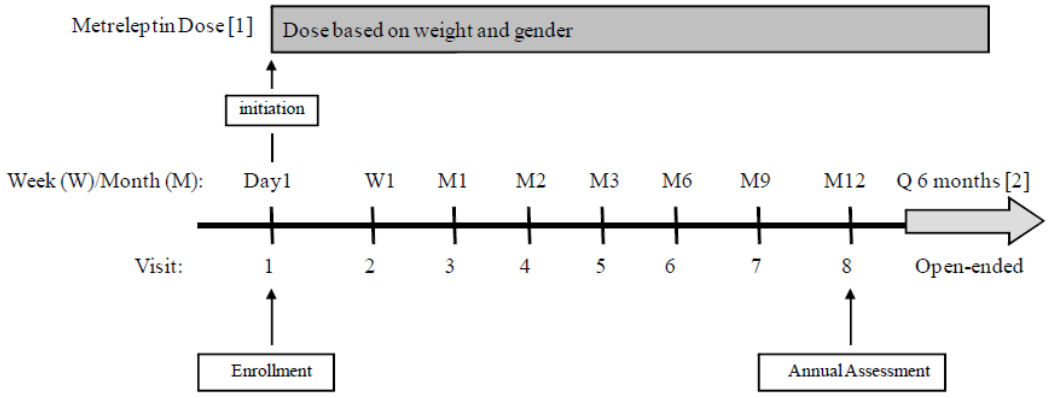
FHA101 Trial

The FHA101 trial was initiated under a treatment IND in 2008 in order to provide expanded access to lipodystrophy patients while the sponsor prepared the data needed for the BLA submission.

FHA101 differed from the NIH trials in several respects; therefore, data from FHA101 were considered by the sponsor to be supplemental in nature: (1) the majority of patients enrolled in FHA101 were patients with partial lipodystrophy, (2) eligibility criteria did not include leptin concentrations, (3) compared to patients in the NIH protocol (initiated in 2000), patients in FHA101 had a shorter exposure to metreleptin, and (4) the data collected for FHA101 were more limited in scope than for the NIH trials, focusing on key efficacy and safety parameters that are typically collected as part of routine clinical care of patients with diabetes mellitus and/or hypertriglyceridemia.

The protocol for FHA101 is summarized in Section 9.4, and the basic study design including the approach to metreleptin dosing is illustrated in the following schematic:

Figure 7. FHA101 Study Design



[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.

Source: Clinical Efficacy Update, Appendix 2

The protocol has three amendments:

- Amendment 1 included:
    - additional assessments (vital signs and documentation of Tanner stage for pediatric patients)
    - clarification of the minimum age of patients who can enroll
    - instruction regarding height measurement for pediatric patients
- Amendment 2:
    - removed some of the routine laboratory assessments that were not considered necessary from a standard of care perspective and clarified some of the procedures required at standard, maintenance, and unscheduled visits
    - updated the efficacy and safety endpoints [added CBC, vital signs, and Tanner staging], analysis methods, justification of sample size, and blood volume sections
- Amendment 3:
    - simplified the treatment protocol for physicians intending to treat patients with diabetes mellitus and/or hypertriglyceridemia associated with lipodystrophy with metreleptin
    - An addendum to amendment 3 was also added that nearly replicated amendment 2 (prior "research" version). One investigator (Dr. Elif Oral, University of Michigan site) initiated metreleptin treatment for lipodystrophy patients on metreleptin treatment under amendment 2. Sites who have both the resources and interest in carrying out a more research-oriented version of the protocol with specified efficacy and safety assessments could conduct metreleptin treatment under the addendum. To date, Dr. Oral's site is the only one with patients enrolled under the addendum.

Therefore, to clarify, amendment 3 is the simplified treatment protocol and the addendum to amendment 3 is the research-oriented treatment protocol.

6 Review of Efficacy

Efficacy Summary

Without a placebo group or adequate historical control, it is challenging to attribute beneficial changes to metreleptin versus improvements in diet or enhanced compliance with concomitant antihyperglycemic or lipid-lowering medications. Furthermore, a substantial amount of missing data, variable duration of therapy, variation in the timing of efficacy assessments, variable and within-trial adjustment of background therapies, compliance that was not systematically documented, and protocol changes add to the challenges of isolating the effect of metreleptin on metabolic control in this application. Nevertheless, a subgroup of patients appears to have achieved benefits from metreleptin that would be unlikely to have been achieved spontaneously: patients with generalized lipodystrophy (congenital or acquired) with severe insulin resistance resulting in diabetes mellitus and / or severe hypertriglyceridemia not adequately controlled with other therapies. The apparent response of this subgroup overall is consistent with that of the small group of patients from the initial trial 991265, and further, is consistent with the mechanism of action of leptin. Metreleptin appears to treat the insulin resistance of lipodystrophy; to the extent diabetes and hypertriglyceridemia are the result of insulin resistance, metreleptin treatment is associated with improvements in, and in some cases normalization of, metabolic control. The table below highlights the differences at 12 months in the key efficacy endpoints of hemoglobin (Hb) A1c, fasting plasma glucose (FPG), and triglycerides (TG) between the patients with generalized lipodystrophy and patients with partial lipodystrophy. In addition, the improvements are accentuated in those patients with uncontrolled diabetes mellitus (defined here as HbA1c 7% or greater or FPG 126 mg/dL or greater) or severe hypertriglyceridemia (defined here as TG 500 mg/dL or greater), supporting the drug's efficacy in treating these diseases.

Table 7. Key Efficacy Parameters at Baseline and Month 12 in Generalized and Partial Lipodystrophy: All Patients and Patients with Elevated HbA1c, FPG, and TG; NIH Trials

HbA1c, %	All			Baseline HbA1c ≥ 7%		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	29	8.7 (0.4)	-2.0 (0.3)	24	9.3 (0.3)	-2.4 (0.5)
Partial	21	7.5 (0.5)	-0.4 (0.2)	11	9.2 (0.5)	-1.0 (0.4)
Fasting glucose, mg/dL	All			Baseline FPG ≥ 126 mg/dL		
	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)	n	Baseline Mean (SE)	Δ from baseline at Month 12 Mean (SE)
Generalized	31	179.5 (15.9)	-48.3 (16.9)	21	218.6 (17.8)	-82.1 (16.5)
Partial	21	155.8 (19.3)	-32.1 (14.8)	11	220 9 (22.5)	-68.6 (23.2)
TG, mg/dL	All			Baseline TG ≥ 500 mg/dL		
	n	Baseline Median	Δ from baseline at Month 12 Median	n	Baseline Median	Δ from baseline at Month 12 Median
Generalized	30	414.5	-246.5	12	1526.5	-1117.0
Partial	21	357.0	-74.0	7	1237.0	-499.0

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 3

The severity of metabolic abnormalities at baseline was more heterogenous in patients with partial lipodystrophy in the NIH trials and, overall, the observed reductions in HbA1c and TG were less than those observed in patients with generalized lipodystrophy. Furthermore, whereas the majority of patients in the NIH trials with generalized lipodystrophy on concomitant anti-hyperglycemic medications at baseline discontinued or had significant reduction in the doses of anti-hyperglycemics at Month 12, a greater proportion of patients with partial lipodystrophy versus generalized lipodystrophy had anti-hyperglycemic medications added to their regimen or doses increased, including two patients with partial lipodystrophy who added insulin to their regimen by Month 12. Similarly, although the majority of patients on lipid-lowering medications at baseline had regimens unchanged at Month 12, the two patients who discontinued all lipid-lowering medication at Month 12 had generalized lipodystrophy, whereas the six patients whose dose of fibrate was increased or who had a lipid-lowering drug added (fibrate or non-fibrate) at Month 12 had partial lipodystrophy.

Because of the smaller reductions in metabolic parameters and confounding by concomitant medications in patients with partial lipodystrophy, it is unclear if a subgroup of patients with partial lipodystrophy can be clearly identified who may benefit from metreleptin. Baseline fasting leptin could be an important factor, particularly given the observation that lipodystrophy patients in earlier versions of the NIH protocol were selected on the basis of low fasting leptin values (originally defined as less than 4 ng/mL in females and less than 3 ng/mL in males) and appeared to have a more pronounced changes in metabolic parameters during metreleptin treatment.

Over the entire NIH cohort, patients with generalized lipodystrophy had mean (SD) fasting leptin of 1.3 (1.1) ng/mL and those with partial lipodystrophy had a value of 4.9 (3.1) ng/mL. The relationship between baseline leptin and changes in metabolic parameters associated with metreleptin treatment was specifically evaluated in patients with partial lipodystrophy who had a wider range of baseline leptin values compared with patients with generalized lipodystrophy who almost all had “low” leptin levels. Across all three endpoints (i.e., HbA1c, FPG, and TG), a greater change from baseline was observed for patients with low baseline leptin concentration in patients with partial lipodystrophy (Table 8). For example, while the average change from baseline in HbA1c at Month 12 was -0.9% for patients with partial lipodystrophy and low leptin levels, it was only -0.1% for patients with partial lipodystrophy and higher leptin levels.

Table 8. Change From Baseline to Month 12 in Key Efficacy Parameters by Leptin Categories; NIH Trials

	Mean (SE) HbA1c (%)			Mean (SE) FPG (mg/dL)			Median TG (mg/dL)		
	N	Baseline	Δ from BL at Mo 12	N	Baseline	Δ from BL at Mo 12	N	Baseline	Δ from BL at Mo 12
Generalized									
All									
Low leptin	26	8.6 (0.4)	-2.1 (0.3)	28	176 (17)	-48 (18)	28	415	-247
Higher leptin	1	10.1 (na)	-1.6 (na)	1	200 (na)	-134 (na)	1	158	-105
Elevated Baseline	Baseline HbA1c ≥ 6%			Baseline FPG ≥ 126 mg/dL			Baseline TG ≥ 200 mg/dL		
Low leptin	23	9.1 (0.4)	-2.4 (0.3)	18	219 (20)	-87 (18)	20	562	-395
Higher leptin	1	10.1 (na)	-1.6 (na)	1	200 (na)	-134 (na)	-	-	-
Partial									
All									
Low leptin	10	7.6 (0.9)	-0.9 (0.4)	10	178 (33)	-56 (27)	10	609	-237
Higher leptin	11	7.5 (0.5)	-0.1 (0.2)	11	136 (22)	-11 (13)	11	343	-64
Elevated Baseline	Baseline HbA1c ≥ 6%			Baseline FPG ≥ 126 mg/dL			Baseline TG ≥ 200 mg/dL		
Low leptin	6	9.2 (1.0)	-1.6 (0.4)	6	239 (36)	-99 (34)	8	1020	-429
Higher leptin	8	8.1 (0.5)	-0.2 (0.2)	5	199 (26)	-32 (24)	8	358	-65

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 5

In summary, replacement or supplementation of leptin with metreleptin is associated with improvements in the metabolic complications of lipodystrophy, although importantly, it does not treat the underlying disorder. Patients with generalized forms of lipodystrophy and significant insulin resistance appear to achieve the best results, including large and in some cases sustained improvements in HbA1c and TG, often accompanied by a discontinuation or decrease of anti-hyperglycemic or lipid-lowering therapies.

By contrast, patients with partial forms of lipodystrophy have a more varied, attenuated, and confounded response. There may be a subset of patients with partial lipodystrophy with very low leptin concentrations and significant metabolic disease that responds to metreleptin, although confounders and missing data present challenges that may be very difficult to overcome in a trial that lacks a comparator.

6.1 Indication

Treatment of metabolic disorders associated with lipodystrophy (see proposed language in Section 2.1, Product Information).

6.1.1 Methods

The statistical analysis plan provided for the NIH trials was written by the sponsor in 2010; therefore, all efficacy analyses are considered to be post-hoc.

The pivotal efficacy data are based on 72 patients with lipodystrophy treated with metreleptin in two open-label, investigator-sponsored trials conducted at the NIH: Study

991265 (completed) and Study 20010769 (ongoing). These 72 patients constitute the Intent-to-Treat (ITT) population, defined as having received at least one dose of metreleptin. Supporting efficacy data are based on 28 patients with lipodystrophy treated with metreleptin under a treatment IND at three sites (with 25 patients enrolled at the University of Michigan site) as of a data cutoff of 07 Mar 2012.

The efficacy review focuses on the trials conducted in the lipodystrophy population: NIH 991265/20010769 (hereafter referred to as the NIH trials, unless one of the two NIH trials is specifically being discussed), and FHA101.

Although additional evaluation of metreleptin efficacy was conducted by the sponsor and various researchers for a variety of conditions, including multi-factorial obesity, obesity associated with congenital leptin deficiency, severe insulin resistance, and others (see Table 41 in Section 7.1.1), the efficacy of metreleptin in these conditions may not be relevant to the proposed indication under this BLA, and therefore, will not be extensively addressed. Available safety findings from these investigational programs are reviewed under Section 7.

6.1.2 Demographics

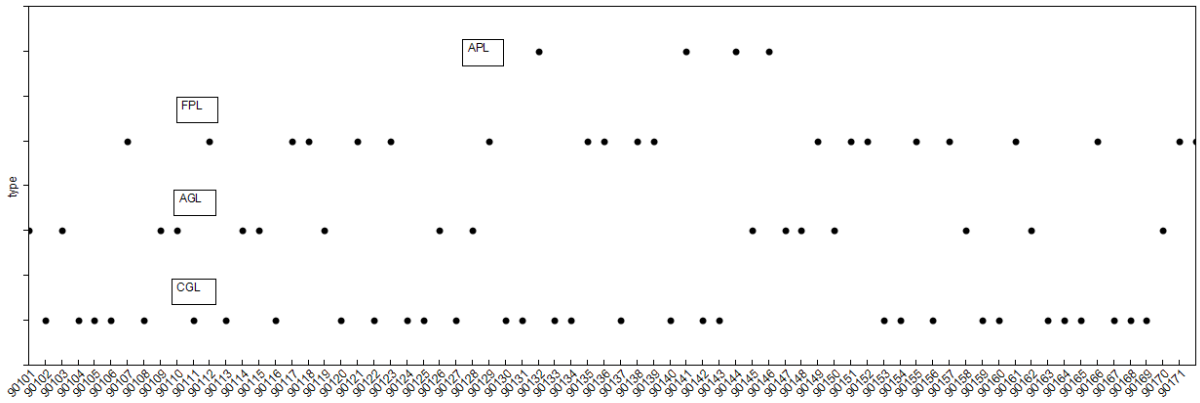
NIH Trials

The overall population was predominantly female (83%) and white (61%). There were no male patients enrolled with partial lipodystrophy. More patients had generalized than partial lipodystrophy, and congenital / familial lipodystrophy was more prevalent than acquired types. Patients diagnosed with generalized lipodystrophy were, on average, younger than those diagnosed with partial lipodystrophy. Similar numbers of pediatric (less than 18 years of age) and adult (18 years of age or older) patients were enrolled.

The following figure illustrates the enrollment of the NIH patients by lipodystrophy type.[§§] Note that patients were enrolled in order of patient number. Over time, more patients with partial lipodystrophy were enrolled. This is likely a reflection of the progressive loosening of leptin concentration inclusion criteria over the course of the ongoing enrollment.

[§§] Reviewer comment: Of note, two of the patients with FPL are sisters (90112 and 90117) and one (90123) is their cousin. This information was not reported in the clinical efficacy documents in the BLA, but was reported in Park, et al (reference 17).

Figure 8. NIH Enrollment



Source: Reviewer generated from BLA 125390 datasets

Metabolic abnormalities tended to be more severe in female patients, as compared to males. Among females, HbA1c elevation was more severe in patients with generalized lipodystrophy than than those with partial lipodystrophy. Female patients with partial lipodystrophy had higher baseline mean TG than those with generalized lipodystrophy (male or female), while female patients with generalized lipodystrophy had the highest proportion of patients with TG 1000 mg/dL or greater.

The following table enumerates demographics and baseline characteristics of patients in the trials by generalized lipodystrophy, partial lipodystrophy, and overall. The table that follows provides an enumeration of medical history by lipodystrophy subtype.

Table 9. Demographics and Baseline Characteristics by Generalized and Partial Lipodystrophy, NIH Trials

	Generalized N=48	**Partial N=24**	**Total N=72**
Sex, n (%)			
Male	12 (25.0)	0	12 (16.7)
Female	36 (75.0)	24 (100)	60 (83.3)
Race, n (%)			
White	22 (45.8)	22 (91.7)	44 (61.1)
Black	9 (18.8)	0	9 (12.5)
Asian	2 (4.2)	1 (4.2)	3 (4.2)
Native American	2 (4.2)	0	2 (2.8)
Hispanic	10 (20.8)	0	10 (13.9)
Other	3 (6.3)	1 (4.2)	5 (5.6)
Age (years)			
Mean (SD)	18.7 (14.0)	33.7 (16.0)	23.7 (16.2)
Min, Max	1, 68	2, 64	1, 68
Age Group, n (%)			

≤ 12	14 (29.2)	3 (12.5)	17 (23.6)
> 12 - < 18	21 (43.8)	1 (4.2)	22 (30.6)
≥ 18 - ≤ 65	12 (25.0)	20 (83.3)	32 (44.4)
> 65	1 (2.1)	0	1 (1.4)
< 18	35 (73.0)	4 (16.7)	39 (54.2)
≥ 18	13 (27.1)	20 (83.3)	33 (45.8)
Lipodystrophy Type			
Congenital/Familial	32 (66.7)	20 (83.3)	52 (72.2)
Acquired	16 (33.3)	4 (16.7)	20 (27.8)
Fasting Leptin (ng/mL) †			
Mean (SD)	1.3 (1.1)	4.9 (3.1)	2.6 (2.6)
Min, Max	0.3, 5.2	1.0, 14.1	0.3, 14.1
Leptin Categories, n (%)			
Lower (M < 2, F < 4)	42 (87.5)	11 (45.8)	53 (73.6)
Higher (M ≥ 2, F ≥ 4)	2 (4.2)	13 (54.2)	15 (20.8)
HbA1c (%)			
Mean (SD)	8.5 (2.1)	7.7 (2.2)	8.2 (2.2)
Min, Max	4.5, 13.7	4.6, 13.3	4.5, 13.7
HbA1c Categories, n (%)			
< 6	8 (16.7)	7 (29.2)	15 (20.8)
≥ 6 to < 7	2 (4.2)	4 (16.7)	6 (8.3)
≥ 7 to < 9	18 (37.5)	6 (25.0)	24 (33.3)
≥ 9	19 (39.6)	7 (29.2)	26 (36.1)
Fasting Plasma Glucose (FPG)			
Mean (SD)	183.9 (86.8)	162.3 (93.0)	176.7 (88.8)
Min, Max	71, 478	49, 367	49, 478
FPG Categories, n (%)			
< 100	7 (14.6)	8 (33.3)	15 (20.8)
≥ 100 to < 126	8 (16.7)	3 (12.5)	11 (15.3)
≥ 126	33 (68.8)	13 (54.2)	46 (63.9)
Fasting TG (mg/dL)			
Mean (SD)	858.7 (1312.8)	1398.8 (3091.5)	1041.3 (2083.1)
Median	368.0	358.0	359.0
Min, Max	49, 7420	101, 12697	49, 12697
Fasting TG Categories, n (%)			
< 200	12 (25.0)	5 (20.8)	17 (23.6)
≥ 200 to < 350	10 (20.8)	6 (25.0)	16 (22.2)
≥ 350 to < 500	8 (16.7)	6 (20.8)	13 (18.1)
≥ 500 to < 1000	6 (12.5)	3 (12.5)	9 (12.5)
≥ 1000	11 (22.9)	5 (20.8)	16 (22.2)
HbA1c and TG Categories, n (%)			
A1c < 6 AND TG < 200	5 (10.4)	2 (8.3)	7 (9.7)
A1c < 6 AND TG ≥ 200	3 (6.3)	5 (20.8)	8 (11.1)
A1c ≥ 6 AND TG < 200	7 (14.6)	3 (12.5)	10 (13.9)
A1c ≥ 6 AND TG ≥ 200	31 (64.6)	14 (58.3)	45 (62.5)

A1c ≥ 6 OR TG ≥ 200	43 (89.6)	22 (91.7)	65 (90.3)
A1c ≥ 7 OR TG ≥ 350	41 (85.4)	20 (83.3)	61 (84.7)
ALT (U/L)			
Mean (SD)	115.0 (123.0)	58.2 (59.7)	96.1 (109.4)
Min, Max	18, 726	16, 232	16, 726
ALT Categories, n (%)			
< 41	12 (25.0)	14 (58.3)	26 (36.1)
≥ 41	36 (75.0)	10 (41.7)	46 (63.9)
AST (U/L)			
Mean (SD)	81.5 (78.6)	40.6 (37.1)	67.9 (70.1)
Min, Max	15, 380	9, 153	9, 380
AST Categories, n (%)			
< 34	16 (33.3)	16 (66.7)	32 (44.4)
≥ 34	32 (66.7)	8 (33.3)	40 (55.6)

* Lower limit of quantitation (LLOQ) for leptin concentration is 0.3 ng/mL; values < LLOQ are reported as 0.3 ng/mL
† The entry criteria for leptin evolved over time. Initially < 4.0 ng/mL [females] or < 3.0 ng/mL [males]) and in 2008 amended to < 12.0 ng/mL in females ≥ 5 yrs and < 8.0 ng/mL in males ≥ 5 yrs, and < 6 ng/mL in 6 mos to < 5 yrs.

Source: Clinical Efficacy Update, Table 6

Table 10. Relevant Medical History by Lipodystrophy Subtype

Medical Term	AGL (N = 16) n (%)	CGL (N = 32) n (%)	APL (N = 4) n (%)	FPL (N = 20) n (%)	All Subjects (N = 72) n (%)
DIABETES MELLITUS	11 (68.8)	25 (78.1)	3 (75.0)	19 (95.0)	58 (80.6)
HYPERTRIGLYCERIDEMIA	8 (50.0)	19 (59.4)	3 (75.0)	17 (85.0)	47 (65.3)
ACANTHOSIS NIGRICANS	7 (43.8)	25 (78.1)	4 (100.0)	4 (20.0)	40 (55.6)
STEATOHEPATITIS	10 (62.5)	10 (31.3)	4 (100.0)	8 (40.0)	32 (44.4)
HEPATOMEGALY	7 (43.8)	17 (53.1)	1 (25.0)	5 (25.0)	30 (41.7)
HYPERTENSION	2 (12.5)	14 (43.8)	1 (25.0)	11 (55.0)	28 (38.9)
PROTEINURIA	8 (50.0)	13 (40.6)	1 (25.0)	2 (10.0)	24 (33.3)
HYPERLIPIDEMIA	4 (25.0)	8 (25.0)	1 (25.0)	5 (25.0)	18 (25.0)
PANCREATITIS	4 (25.0)	4 (12.5)	1 (25.0)	7 (35.0)	16 (22.2)
INSULIN RESISTANCE	1 (6.3)	7 (21.9)	2 (50.0)	5 (25.0)	15 (20.8)
HEPATIC STEATOSIS	2 (12.5)	6 (18.8)	0 (0.0)	6 (30.0)	14 (19.4)
DEPRESSION	3 (18.8)	5 (15.6)	0 (0.0)	4 (20.0)	12 (16.7)
POLYCYSTIC OVARY SYNDROME	1 (6.3)	4 (12.5)	1 (25.0)	6 (30.0)	12 (16.7)
AMENORRHEA	3 (18.8)	5 (15.6)	0 (0.0)	3 (15.0)	11 (15.3)
HEADACHES	2 (12.5)	7 (21.9)	1 (25.0)	1 (5.0)	11 (15.3)
HIRSUTISM	0 (0.0)	6 (18.8)	1 (25.0)	4 (20.0)	11 (15.3)
HEPATOSPLENOMEGALY	3 (18.8)	5 (15.6)	0 (0.0)	0 (0.0)	8 (11.1)
XANTHOMAS	2 (12.5)	2 (6.3)	0 (0.0)	4 (20.0)	8 (11.1)
ANEMIA	2 (12.5)	2 (6.3)	0 (0.0)	3 (15.0)	7 (9.7)
HYPERCHOLESTEROLEMIA	1 (6.3)	5 (15.6)	0 (0.0)	1 (5.0)	7 (9.7)
VITAMIN D DEFICIENCY	2 (12.5)	4 (12.5)	0 (0.0)	1 (5.0)	7 (9.7)
ASTHMA	3 (18.8)	2 (6.3)	0 (0.0)	1 (5.0)	6 (8.3)
CIRRHOSIS	1 (6.3)	5 (15.6)	0 (0.0)	0 (0.0)	6 (8.3)
FATIGUE	3 (18.8)	1 (3.1)	0 (0.0)	2 (10.0)	6 (8.3)
NEUROPATHY	2 (12.5)	2 (6.3)	1 (25.0)	1 (5.0)	6 (8.3)
DIABETIC RETINOPATHY	0 (0.0)	1 (3.1)	0 (0.0)	4 (20.0)	5 (6.9)
OVARIAN CYSTS	1 (6.3)	2 (6.3)	0 (0.0)	2 (10.0)	5 (6.9)

Note: - Relevant medical history terms were identified by a sponsor review.

Source: Clinical Efficacy Update, Supporting Data Summary 1.4

Seven patients were enrolled with baseline HbA1c less than 6% and TG less than 200 mg/dL (see Table 11 below). [Recall that patients in the NIH trials had to have either: diabetes mellitus (1997 criteria), fasting insulin greater than 30 µU/mL, or fasting TG greater than 200 mg/dL, therefore, presumably patients in this group would have been

enrolled based on insulin resistance.] Six of the seven patients with baseline HbA1c less than 6% and TG less than 200 mg/dL were pediatric (age less than 18 years), five of whom were less than 12 years old. The one adult patient (90157) with normal HbA1c and TG at baseline had a history of diabetes and hypertriglyceridemia but good metabolic control at the baseline assessment. All seven patients had elevated baseline ALT (41 U/L or greater) and/or AST (34 U/L or greater) or had a history of hepatomegaly, hepatic steatosis, and/or steatohepatitis.[***] Patient 90165 (2-year-old female with CGL, see bolded row in the table below) had only a mildly elevated AST and a history of hepatic steatosis without diabetes, hypertriglyceridemia, or insulin resistance.[†††]

Table 11. Baseline Characteristics of Patients Enrolled with HbA1c Less than 6% and TG Less than 200 mg/dL

Patient	Age	Sex	Subtype	Insulin (µU/mL)	ALT (U/L)	AST (U/L)	FPG (mg/dL)	HbA1c (%)	TG (mg/dL)	Leptin (ng/mL)
90131	9	M	CGL	43.9	177	85	79	4.5	137	0.5
90134	9	M	CGL	110	386	258	71	5.5	122	0.5
90144	10	F	APL	57.6	90	48	80	4.6	108	1.12
90150	11	M	AGL	89.6	726	380	105	5	141	0.46
90157	30	F	FPL	25.7	68	35	83	5.3	101	4.61
90160	14	F	CGL	79	55	28	95	5.6	117	NA
90165	**2**	**F**	**CGL**	**6.6**	**28**	**37**	**90**	**4.9**	**193**	**2.41**

Source: Reviewer derived from BLA datasets (Clinical Safety Update, DLABS 2)

Additional examples of patients with outlier laboratory values at baseline include: (1) a qualifying leptin concentration for one patient (90146, 27-year-old female with APL) that exceeded 12 ng/mL; the investigator allowed the patient to enroll based on an earlier value reported to be 12 ng/mL,[‡‡‡] and (2) one patient (90150, 11-year-old male with AGL) had very high liver enzymes at baseline (ALT 726 U/L and AST 380 U/L).

[***] It was stated that the investigator generally enrolled patients with insulin resistance only if they also presented with clinically significant liver disease - reported as hepatic steatosis and/or steatohepatitis - although it is unknown if these patients received liver biopsy in order to make these diagnoses.

[†††] Although the sponsor states that the inclusion of Patient 90165 was consistent with the protocol inclusion criteria for patients age 5 years or younger, I could not find that the requirement for metabolic abnormalities (diabetes, fasting insulin > 30 µU/mL, or hypertriglyceridemia) was changed when patients younger than 5 years of age were allowed to enter the trial in a later protocol amendment (in fact, the triglyceride criteria was changed to accommodate the fact that fasting TG would not be able to be obtained in infants). Therefore, her inclusion in the trial with no history of diabetes mellitus and baseline laboratory values of FPG 90 mg/dL, HbA1c 4.9%, TG 193 mg/dL, and insulin 6.6 µU/mL, appears to have been a protocol violation.

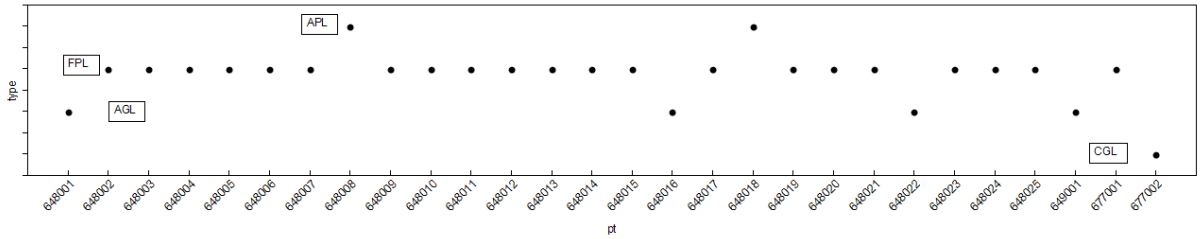
[‡‡‡] Nevertheless, this is a protocol violation.

FHA101 Trial

Of the 28 patients enrolled in the trial by the 7 Mar 2012 datacut, the population was predominantly female (92.9%) and white (75.0%). Five (18%) were diagnosed with generalized lipodystrophy (one congenital and four acquired), and 23 (82%) patients were diagnosed with partial lipodystrophy (21 familial and two acquired). The two male patients enrolled in the trial were diagnosed with AGL and FPL, respectively. Of 28 patients, 25 (89%) were 18 years or older. Patients diagnosed with generalized lipodystrophy were, on average, younger than the patients diagnosed with partial lipodystrophy (26 ± 24 years and 48 ± 12 years, respectively).

The following figure illustrates the patients enrolled in FHA101 by lipodystrophy diagnosis:

Figure 9. FHA101 Enrollment



Source: Reviewer generated from BLA 125390 datasets

A total of 24 (86%) patients had an HbA1c 6% or greater; 75% had an HbA1c 7% or greater, and 32% had an HbA1c 9% or greater. In addition, 18 (64%) patients had a TG value 200 mg/dL or greater, eight (35%) patients had TG 350 mg/dL or greater, and five (18%) patients had TG 500 mg/dL or greater.

Of the 28 ITT patients, 27 (96%) had either a baseline HbA1c 6% or greater or TG 200 mg/dL or greater. One patient (648019) had a baseline HbA1c of 5.6% and TG of 79 mg/dL, but according to the investigator had a history of hypertriglyceridemia (TG values within 1.5 years prior to starting metreleptin ranging from 212 mg/dL to 319 mg/dL).[§§§] The patient was intolerant to statins and had fatty liver disease. Approximately 82% of the patients had HbA1c 7% or greater or fasting TG 350 mg/dL or greater.

Compared to the NIH patients, FHA101 patients had a higher mean baseline fasting leptin concentration (12.9 ng/mL versus 2.6 ng/mL), consistent with (1) the higher proportion of partial lipodystrophy patients enrolled in FHA101, and (2) leptin concentrations as inclusion criteria in the NIH trials, but not in FHA101.

[§§§] This is a protocol violation, and highlights the fluctuation in TG even off of metreleptin.

Other demographic information and baseline characteristics can be found in the table below.

Table 12. Demographics and Baseline Characteristics by Generalized and Partial Lipodystrophy, FHA101 Trial

	Generalized N=5	**Partial N=23**	**Total N=29**
Sex, n (%)			
Male	1 (20.0)	1 (4.3)	2 (7.1)
Female	4 (80.0)	22 (95.7)	26 (92.9)
Race, n (%)			
White	4 (80.0)	17 (73.9)	21 (75.0)
Black	1 (20.0)	2 (8.7)	3 (10.7)
Native American	0	1 (4.3)	1 (3.6)
Hispanic	0	1 (4.3)	1 (3.6)
Other	0	2 (8.7)	2 (7.1)
Age (years)			
Mean (SD)	25.6 (24.0)	47.5 (12.3)	43.6 (16.8)
Min, Max	9, 67	23, 67	9, 67
Age Group, n (%)			
≤ 12	2 (40.0)	0	2 (7.1)
> 12 - < 18	1 (20.0)	0	1 (3.6)
≥ 18 - ≤ 65	1 (20.0)	22 (95.7)	23 (82.1)
> 65	1 (20.0)	1 (4.3)	2 (7.1)
Lipodystrophy Type			
Congenital/Familial	1 (20.0)	21 (91.3)	22 (78.6)
Acquired	4 (80.0)	2 (8.7)	6 (21.4)
Fasting Leptin (ng/mL) †			
Mean (SD)	0.7 (0.0)	14.8 (10.3)	12.9 (10.7)
Min, Max	0.7, 0.7	1.4, 42.9	0.7, 42.9
HbA1c (%)			
Mean (SD)	8.6 (1.9)	7.9 (1.5)	8.0 (1.6)
Min, Max	5.5, 10.2	5.6, 11.1	5.5, 11.1
HbA1c Categories, n (%)			
< 6	1 (20.0)	3 (13.0)	4 (14.3)
≥ 6 to < 7	0	3 (13.0)	3 (10.7)
≥ 7 to < 9	1 (20.0)	11 (47.8)	12 (42.9)
≥ 9	3 (60.0)	6 (26.1)	9 (32.1)
Fasting TG (mg/dL)			
Mean (SD)	3248.0 (4973.5)	401.9 (537.1)	823.6 (2039.6)
Median	1099.5	255.0	257.0
Min, Max	170.0, 10623.0	66.0, 2540.0	66.0, 10623.0
Fasting TG Categories, n (%)			
< 200	1 (20.0)	3 (13.0)	4 (14.3)

≥ 200 to < 350	0	10 (43.5)	10 (35.7)
≥ 350 to < 500	1 (20.0)	2 (8.7)	3 (10.7)
≥ 500 to < 1000	0	1 (4.3)	1 (3.6)
≥ 1000	2 (40.0)	2 (8.7)	4 (14.3)
HbA1c and TG Categories, n (%)			
A1c < 6 AND TG < 200	0	1 (4.3)	1 (3.6)
A1c < 6 AND TG ≥ 200	1 (20.0)	2 (8.7)	3 (10.7)
A1c ≥ 6 AND TG < 200	1 (20.0)	7 (30.4)	8 (28.6)
A1c ≥ 6 AND TG ≥ 200	2 (40.0)	13 (56.5)	15 (53.6)
A1c ≥ 6 OR TG ≥ 200	5 (100.0)	22 (95.7)	27 (96.4)
A1c ≥ 7 OR TG ≥ 350	5 (100.0)	18 (78.3)	23 (82.1)
* Lower limit of quantitation (LLOQ) for leptin concentration is 0.7 ng/mL; values < LLOQ are reported as 0.7 ng/mL † Leptin data are not available for 6 of 28 patients			

Source: Clinical Efficacy Update, Table 35

6.1.3 Subject Disposition

NIH Trials

Seven of the nine patients enrolled in NIH study 991265 also enrolled in 200010769. As of the 11 Jul 2011 cutoff, 52 (72%) of 72 patients enrolled in the NIH trial were still actively participating.

The most common reason for withdrawal was "other" for eight (11.1%) patients (one for "stress", one for "health issues", and six were transferred to Named Patient Programs in their respective countries), followed by "noncompliance" for four (5.6%) patients.[****]

Reviewer comment: The reasons for withdrawal for "stress" and "health issues" under "other" reasons should have been considered adverse events.

Two patients withdrew because they were deemed ineligible to continue participation in the study, including one patient (90115) due to a diagnosis of peripheral T-cell lymphoma and one patient (90126) due to the investigator's assessment that the patient was no longer appropriate to continue in the study due to the need to undergo treatment for an adverse event (deep vein thrombosis).

Reviewer comment: The reasons for withdrawal for "ineligibility" should have been considered adverse events.

[****] The sponsor identified these 4 patients as: 90118, 90121, 90127, and 90146. However, Patient 90102 was also identified in the database as discontinuing due to non-compliance. This patient may have had a contributing adverse event (worsening renal function) that was not documented. See Section 7.3.5, Submission Specific Primary Safety Concerns.

A total of five patients were reported to have withdrawn due to adverse events, including deaths:

- Two patients (90147 and 90114[††††]) were withdrawn due to a non-fatal adverse event (peripheral T-cell lymphoma and proteinuria, respectively).

- Three patients experienced serious adverse events that led to death (90125, pancreatitis with a ruptured pseudocyst, leading to septic shock and subsequent cardiac arrest; 90106, renal failure and subsequent cardiac arrest; and 90158, chronic hepatic failure). These adverse events are described further in Section 7.3.1, Deaths.

Table 13. Patient Disposition for NIH Trials as of 11 July 2011

Disposition [1]	**All Patients, N=72 n (%)**
Enrolled in Study 991265	9 (12.5)
Withdrew from Study 991265	1 (1.4)
Enrolled in Study 20010769	70 (97.2)
Previously Treated in 991265 Prior to Enrolling in 20010769 [2]	7 (9.7)
Enrolled Directly into 20010769	63 (87.5)
Active in Study 20010769	52 (72.2)
Withdrew from Study 20010769	18 (25.0)
Primary Reason for Withdrawal in Studies 991265/20010769	
Other [3]	8 (11.1)
Adverse Event [4][5]	5 (6.9)
Noncompliance	4 (5.6)****
Ineligibility Determined	2 (2.8)
Consent Withdrawn	0
Administrative Decision	0
Lost to Follow Up	0

[1] Disposition of each patient is based on the data at the end of Study 991265 or as of the 11 July 2011 data cutoff for Study 20010769
[2] Includes 6 patients who completed Study 991265 and 1 patient (90105) who withdrew from Study 991265 but later enrolled into Study 20010769.
[3] Includes 6 patients who transferred to a named patient program, 1 patient due to "stress", and 1 patient due to "health issues"
[4] Includes 1 patient (90114) from Study 20010769 who was withdrawn from metreleptin due to event of proteinuria, but was re-initiated on metreleptin 3 months later, and subsequently transferred to a named patient program.
[5] Includes 3 withdrawals due to death.

Source: BLA 126390 Clinical Efficacy Update, Table 5

[††††] Patient 90114 was previously captured in Study 20010769 as discontinuation due to an adverse event. During data collection for the 120-Day Safety Update (January 2013), it was determined that the patient had not been discontinued and had resumed metreleptin therapy under study 20010769 after being off drug for 19 months. Upon resumption of dosing, the patient remained on metreleptin for 19 months and then reportedly left 20010769 to transfer into the compassionate use Named Patient Program in England.

Reviewer comments:

1. ***As noted above, some discontinuations categorized for other reasons should have been captured as adverse events leading to withdrawal.***

2. ***As of the 31 July 2009 data cut-off, five patients were reported discontinued due to non-compliance (the table above reports four).**** It was also reported that eight of nine patients in study 991265 enrolled in study 20010769 (the table above reports seven).***[‡‡‡‡]

As of the 11 Jul 2011 data cutoff, total exposure to metreleptin (excluding dosing gaps) for 72 NIH patients ranged from two months to approximately 11 years, with a median exposure of approximately 2.7 years, and with 60 (83%) patients having had exposure longer than one year. Forty-five patients were exposed for more than one year and up to six years, and 15 patients had more than six years of metreleptin exposure.

A total of 16 (22%) patients had dosing gaps that were excluded from exposure calculations, which varied from five days to 2,480 days. Four of the 16 patients missed more than one year of metreleptin treatment: 90105 (520 days; noncompliance), 90106 (2,480 days; withdrawal of consent after one year of metreleptin treatment, reinitiated eight years later), 90110 (803 days, due to an adverse event of 'increased LFTs' assessed as related to autoimmune hepatitis), and 90128 (742 days, noncompliance).

For the overall group of patients, the total exposure to metreleptin in the NIH trials was 280 patient-years (PY).

[‡‡‡‡] This discrepancy is attributed to Patient 90103. During the compassionate use exemption (patient consented in June 2001), Patient 90103 had a serious adverse event of elevated liver function tests (December 2001 to January 2002). Although the intent was for this patient to enter Study 20010769, the investigator maintained the patient in Study 991265, but interrupted treatment to allow further assessment and a hepatology consultation. After assessment that the serious adverse event was most likely related to a concomitant medication, the patient re-initiated metreleptin treatment in March 2002 under the compassionate use exemption. Approximately three months after re-initiation of treatment, the patient had a serious adverse event of paranoia and was diagnosed with bipolar disorder (June 2002). Based on the diagnosis of bipolar disorder, the investigator concluded that the patient met an exclusion criterion for Study 20010769 (i.e., psychiatric disorder impeding competence or compliance) and therefore was not eligible to enroll into Study 20010769.

Table 14. Extent of Exposure to Metreleptin in NIH Trials with Dosing Gaps Excluded

Exposure	**All Patients N=72**
Category (years), n (%)	
≤ 0.5	4 (5.6)
> 0.5 to ≤ 1	8 (11.1)
> 1 to ≤ 2	14 (19.4)
> 2 to ≤ 3	14 (19.4)
> 3 to ≤ 4	4 (5.6)
> 4 to ≤ 5	5 (6.9)
> 5 to ≤ 6	7 (9.7)
> 6 to ≤ 7	2 (2.8)
> 7 to ≤ 8	2 (2.8)
> 8 to ≤ 9	5 (6.9)
> 9	7 (9.7)
Exposure (years)	
Mean (SD)	3.89 (3.09)
Median	2.71
Min, Max	0.2, 10.9
Total Exposure in Patient-Years	280.0
Note: Dosing gap is defined as missing one or more days of dosing	

Source: BLA 125390 Clinical Efficacy Update, Table 4

Mean exposure was greatest for CGL (4.3 y), followed by APL and FPL subtypes (3.8 y), and AGL (3.1 y). The total exposure to metreleptin in PY for each lipodystrophy subtype was as follows: CGL (138.2), FPL (76.6), AGL (49.9), and APL (15.3).

There was no systematic collection of treatment compliance data. Therefore, no analyses are available on the percent compliance with metreleptin treatment of individual patients during the treatment period.

FHA101 Trial

As of the 07 Mar 2012 data cutoff, 20 of 28 patients enrolled were still actively participating. The most common reasons for withdrawal were withdrawal of consent and adverse events (three patients each).

Reasons for withdrawal of consent were desire to get pregnant (648004), reason unspecified (648007), and travel burden coupled with lack of efficacy (648013).

Of the three withdrawals due to adverse events, two had a fatal outcome. Patient 648008 experienced a serious adverse event, 'loss of consciousness' (acute bilateral subdural hematomas after a fall), which had a fatal outcome. Patient 649001 experienced a serious adverse event of 'adenocarcinoma', which was a known pre-

existing condition prior to starting metreleptin and which had a fatal outcome. These events are discussed in Section 7.3.1, Deaths. Patient 648021 was withdrawn due to a non-serious event of muscle spasms, which was assessed by the investigator as related to treatment.

Table 15. Patient Disposition for Treatment IND FHA101 as of 07 Mar 2012

Disposition	**All Patients, N=28 n (%)**
Ongoing	20 (71.4)
Withdrew	8 (28.6)
Primary Reason for Withdrawal	
Consent Withdrawn	3 (10.7)
Adverse Event [1]	3 (10.7)
Investigator Decision	1 (3.6)
Protocol Violation	0
Lost to Follow Up	1 (3.6)
[1] Including deaths	

Source: Clinical Efficacy Update, Table 34

As of the 07 Mar 2012 cutoff for this update, total exposure to metreleptin for the 28 FHA101 patients ranged from 0.1 years to approximately three years, with a median exposure of approximately one year. The total exposure to metreleptin in the FHA101 study was 34.7 PY. Of the 28 patients, 15 patients had exposure longer than one year and six patients had exposure of two or more years.

The extent of exposure to metreleptin in FHA101 is presented in the table below.

Table 16. Extent of Exposure to Study Medication, FHA101

Exposure	**All Patients, N=28 n (%)**
Category (years), n (%)	
≤ 0.5	8 (28.6)
> 0.5 to ≤ 1	5 (17.9)
> 1 to ≤ 2	9 (32.1)
> 2 to ≤ 3	6 (21.4)
Exposure (years)	
Mean (SD)	1.24 (0.897)
Median	1.03
Min, Max	0.1, 2.9
Total Exposure in Patient-Years	34.7
Note: Dose gaps are not excluded	

Source: Clinical Efficacy Update, Table 33

Mean exposure was greatest for patients with FPL and AGL (1.3 y) followed by CGL and APL (0.6 y) subtypes. The total exposure to metreleptin in PY for each lipodystrophy subtype was as follows: FPL (27.9), AGL (5.0), APL (1.2), and CGL (0.6).

6.1.4 Analysis of Primary Endpoints

Hemoglobin A1c, Fasting Plasma Glucose, and Fasting Triglycerides

Key efficacy endpoints were considered to be HbA1c, fasting plasma glucose (FPG), and fasting TG. These endpoints, as well as fasting lipids, ALT, and AST (see Section 6.1.5), were summarized over the first 12 months of treatment.

Reviewer comment: The limitations to summarizing the data are numerous, given that individual patients may or may not "respond"[§§§§] to the intervention due to issues with compliance to metreleptin, diet, or concomitant medications in addition to changes to background therapy after starting treatment (for example, should a patient be considered a 12-month "responder" for improvement in triglycerides if she was newly started on fenofibrate prior to the 12-month visit?).

NIH Trials

Although longer-term efficacy data are available for some patients (maximum metreleptin exposure up to 11 years), the sponsor focused on results up to 12 months since this was felt to provide the best balance of the number of patients with available data and the duration of treatment.

Reviewer comment: Although I agree with the sponsor's rationale for conducting the primary efficacy evaluation on the first 12 months of data, this is problematic in cases where patients have missing data the first year, or in cases where there is a lot of variability in response over time, or when medication changes were made during the first year.

Although 60 patients had exposure exceeding one year, only 51 of those patients had efficacy data to summarize at Month 12.[*****] The nine patients missing Month 12 efficacy data had a visit prior to Month 12, and six of these had a visit subsequent to the Month 12 visit.

Reviewer comment: Given the substantial amount of missing data, I have some concern that the observed changes from baseline are an overestimate.

[§§§§] Definitions of a positive response are arbitrary, since they were not pre-specified.
[*****] One patient (90167) had exposure just shy of one year and thus not counted as exceeding one year but had data at the 12 Month visit, bringing total N at Month 12 to 52.

On average, patients treated in the NIH trials had reductions from baseline in HbA1c and FPG that were apparent at Month 4, Month 8, and Month 12, see Table 17. At Month 12, mean HbA1c decreased by 1.4% (95% CI: -1.8, -0.9) from a baseline of 8.2%, and mean FPG decreased by 41.8 mg/dL (95% CI: -65.2, -18.4) from a baseline of 169.8 mg/dL.

On average, treatment with metreleptin was associated with statistically significant reductions from baseline in fasting TG that were apparent at Month 4 and Month 12, but not at Month 8. At Month 12, the median percent change from baseline in TG was -44.8.

Table 17. Change From Baseline Month 4, 8, and 12 in HbA1c, FPG, and Fasting TG (NIH Trials)

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.

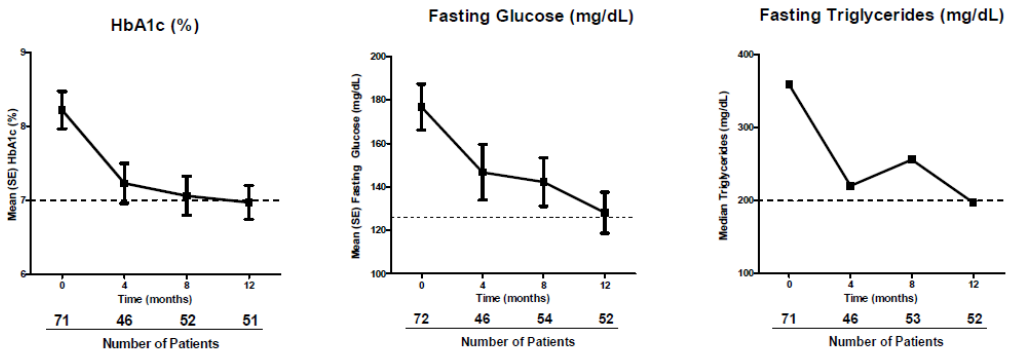
Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 8

Mean ± SE for HbA1c and FPG values and median values for fasting TG at baseline, Month 4, Month 8, and Month 12 are presented in Figure 10 for patients with observed data at each time point.

From a baseline HbA1c of 8.2 ± 0.3%, mean HbA1c values were 7.2 ± 0.3% at Month 4 and 6.9 ± 0.2% at Month 12. From a baseline FPG of 177 ± 10 mg/dL, mean FPG was 147 ± 13 mg/dL at Month 4 and 128 ± 9 mg/dL at Month 12.

TG concentrations were not normally distributed in this population and included some extreme outlying values, which have disproportionate influence on the mean values; thus median TG concentrations are plotted. From a median baseline TG of 359 mg/dL, median TG concentration was 220 mg/dL at Month 4 and 197 mg/dL at Month 12.

Figure 10. Mean (SE) HbA1c, Mean (SE) FPG, and Median Fasting TG Concentrations Over Time at Baseline and Month 4, 8, and 12 (NIH Trials)



Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 1

The sponsor considered the “completer” analysis the change from baseline in HbA1c, FPG, and fasting TG for those patients who completed at least one year of treatment and had values available for visits at baseline, Month 4, Month 8, and Month 12.

Changes from baseline in this “completer” population were of comparable magnitude and durability to those seen in the “ITT observed” population.

Table 18. Change from Baseline at Month 4, 8, and 12 in HbA1c, FPG, and Fasting TG (NIH; 12-Month Completers)

Parameter	Statistic [1][2][3]	Baseline	Month 4	Month 8	Month 12
HbA1c (%), n = 27			**Change From Baseline**		
	Mean	8.5 (1.8)	-1.2 (0.2)	-1.2 (0.3)	-1.5 (0.3)
	Median	8.7	-0.8	-1.2	-1.4
	Min, Max	5.5, 13.7	-4.0, 0.7	-4.3, 1.3	-4.5, 0.9
FPG (mg/dL), n = 30			**Change From Baseline**		
	Mean	188.4 (85.2)	-36.0 (10.0)	-36.0 (13.1)	-43.4 (15.9)
	Median	175	-34	-43	-46
	Min, Max	71, 478	-143, 125	-149, 165	-225, 271
Fasting TG (mg/dL), n = 29			**Change From Baseline**		
	Mean	1089.1 (284.6)	-470.5 (243.8)	-456.0 (317.2)	-693.5 (236.2)
	Median	471.0	-126.0	-127.0	-263.0
	Min, Max	87, 7420	-5682, 2811	-6814, 4345	-5977, 473
			Percent Change From Baseline		
	Mean	1089.1 (284.6)	-35.6 (7.6)	-22.6 (14.7)	-43.3 (7.4)
	Median	471.0	-42.0	-43.6	-51.3
	Min, Max	87, 7420	-89, 94	-92, 288	-93, 90

[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.

[3] Error is given as SD for baseline value and SE for change from baseline.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 9

Key glycemic (HbA1c) and lipid (TG) efficacy data were analyzed for both the percentage of patients achieving certain targets or achieving certain degree of improvement at specified time points. The following tables focus on the proportion of patients with clinical improvements with the most substantial baseline abnormalities. See Section 6.1.7, below, for an additional discussion of baseline metabolic derangements and improvement over time.

Table 19. Proportion of Patients Achieving HbA1c and TG Targets During Initial 12 Months of Metreleptin Treatment (NIH Trials)

Patients with Baseline HbA1c > 7% Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=46 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=39 n (%)	At Month 12 Time Point N=38 n (%)
HbA1c ≤ 7%	20 (43.5)	13 (33.3)	15 (39.5)
HbA1c ≤ 6.5%	15 (32.6)	11 (28.2)	11 (28.9)
HbA1c ≤ 6%	10 (21.7)	6 (15.4)	8 (21.1)
Decrease from baseline in HbA1c ≥ 0.5%	41 (89.1)	30 (76.9)	33 (86.6)
Decrease from baseline in HbA1c ≥ 1%	37 (80.4)	25 (64.1)	28 (73.7)
Decrease from baseline in HbA1c ≥ 2%	27 (58.7)	16 (41.0)	18 (47.4)
Patients with Baseline TG > 500 mg/dL Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=24 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=20 n (%)	At Month 12 Time Point N=19 n (%)
TG ≤ 500 mg/dL	18 (75.0)	10 (50.0)	12 (63.2)
Decrease from baseline in TG ≥ 20%	24 (100.0)	16 (80.0)	18 (94.7)
Decrease from baseline in TG ≥ 50%	23 (95.8)	12 (60.0)	15 (78.9)
Patients with Baseline TG > 1000 mg/dL Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=15 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=13 n (%)	At Month 12 Time Point N=12 n (%)
TG ≤ 1000 mg/dL	14 (93.3)	7 (53.8)	9 (75.0)
TG ≤ 500 mg/dL	9 (60.0)	3 (23.1)	6 (50.0)
Decrease from baseline in TG ≥ 20%	15 (100.0)	10 (76.9)	12 (100.0)
Decrease from baseline in TG ≥ 50%	15 (100.0)	8 (61.5)	11 (91.7)
Patients with Baseline HbA1c > 7% AND TG > 500 mg/dL Meeting Target			
	At Any Post-Baseline Time Point in First 12 Months N=19 n (%)	At Any Two Consecutive Post-Baseline Time Points in First 12 Months N=16 n (%)	At Month 12 Time Point N=15 n (%)
HbA1c ≤ 7% OR TG ≤ 500 mg/dL	16 (84.2)	10 (62.5)	10 (66.7)
HbA1c ≤ 7% AND TG ≤ 500 mg/dL	6 (31.6)	4 (25.0)	4 (26.7)

Source: Clinical Efficacy Update, Tables 12, 13, and 14

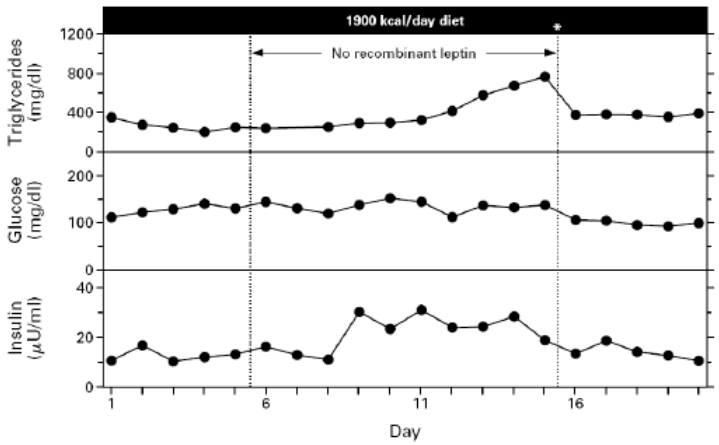
Metreleptin Dechallenge and Rechallenge

Four patients in the NIH trials were evaluated for the effects of stopping and restarting metreleptin. One patient with AGL (90101) underwent an inpatient controlled withdrawal, which was detailed in the publication by Oral, et al.[22] Two patients (90112 and 90117) with FPL underwent controlled withdrawal under the direction of the investigator to specifically test whether metreleptin was still contributing to efficacy in

addition to an insulin regimen that had been titrated to good glycemic control. A fourth patient, 90144, stopped treatment on her own during the second year of treatment and then restarted again. The details of these cases are presented below.

- Patient 90101 was a 17-year-old female with AGL who had a medical history of diabetes, severe hypertriglyceridemia (the use of plasma exchange therapy to treat this patient's severe hypertriglyceridemia is detailed in reference 21), xanthomas, and pancreatitis. The patient's baseline HbA1c and triglycerides were 8% and 7420 mg/dL, respectively. Following eight months of metreleptin treatment, metabolic control improved as evidenced by an HbA1c of 6.3% and TG of 606 mg/dL. At this time, the patient underwent a planned withdrawal of metreleptin treatment during an inpatient admission at the NIH. She was placed on a fixed caloric diet based on her reported food intake during metreleptin treatment and on her resting metabolic rate to rule out interference of changes in food intake on metabolic parameters. After five days in this controlled setting, metreleptin treatment was discontinued while all other medications were kept constant. The figure below illustrates the trajectory of TG, glucose, and insulin values over this period of time. After 15 days of withdrawal of therapy, the patient experienced nausea, vomiting, and abdominal pain consistent with pancreatitis. Resumption of metreleptin therapy returned metabolic parameters (especially TG) to pre-withdrawal concentrations.

Figure 11. Effect of Interruption of Metreleptin Treatment on Metabolic Parameters (Study 991265; Patient 90101)



Source: Clinical Efficacy Update, Figure 12 (adapted from reference 22)

Reviewer comment: This is a very compelling case of metreleptin efficacy in a patient with generalized lipodystrophy and severe insulin resistance. In particular, it is noted that she had metabolic worsening upon discontinuation of metreleptin, despite reportedly clamping energy intake, which would support an independent effect of metreleptin on insulin sensitivity independent of food

intake. Nevertheless, this is only a single case (in the very first NIH patient) and has not been replicated.

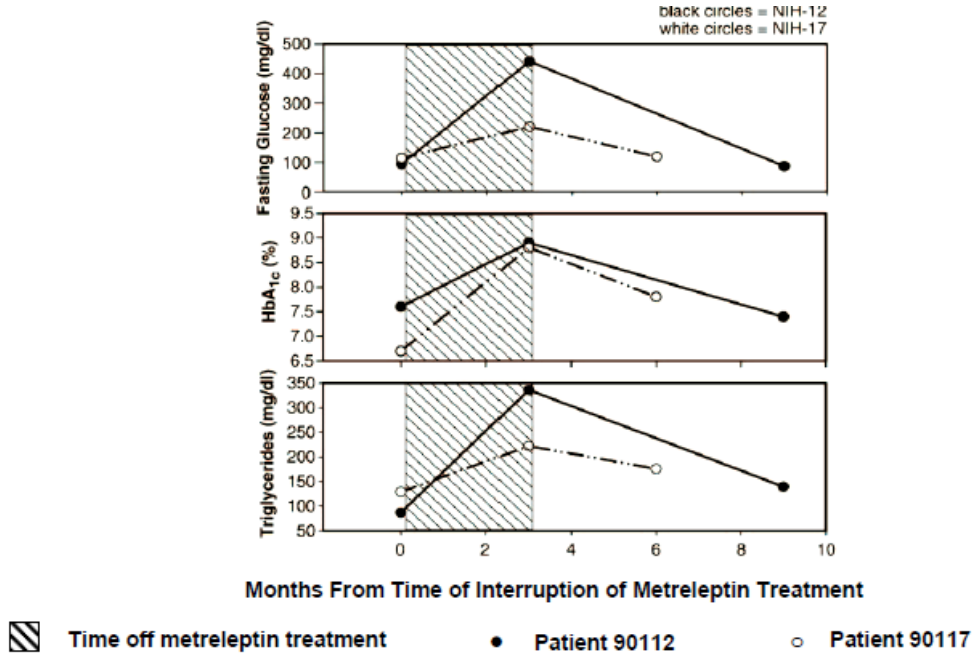
- Patient 90112 was a 64-year-old female with FPL and patient 90117 was a 45-year-old female with FPL. Both patients received metreleptin treatment for approximately 30 months prior to the controlled withdrawal. The table below demonstrates the patients' metabolic parameters prior to metreleptin withdrawal and the figure illustrates the deterioration in metabolic control during the three months that metreleptin treatment was withdrawn. Insulin and oral anti-diabetes and lipid-lowering agents were maintained at the same doses during both the three-month controlled withdrawal and re-initiation of metreleptin periods. Both patients demonstrated improvement in metabolic parameters after re-initiating metreleptin treatment.

Table 20. Individual Metabolic Parameters Prior to Controlled Withdrawal of Metreleptin: NIH Patients 90112 and 90117

Patient Number	Visit	HbA1c (%)	FPG (mg/dL)	TG (mg/dL)
900112	Baseline	9.0	232	198
64 y, F	Month 12	8.4	165	103
FPL	Month 24	6.9	117	88
	Month 30 [1]	7.6	100	87
90117	Baseline	9.7	284	550
45 y, F	Month 12	9.3	196	252
FPL	Month 24	8.0	245	177
	Month 30 [1]	6.7	123	129

[1] Last available value prior to metreleptin withdrawal.
Source: Clinical Efficacy Update, Table 18

Figure 12. Effect of Interruption of Metreleptin Treatment on Metabolic Parameters (Study 20010769; Patients 90112 and 90117)



Both patients were on metreleptin treatment for at least 12 months prior to interruption of treatment (time -= month 0).

Source: Clinical Efficacy Update, Figure 13 (adapted from reference 17)

Reviewer comment: These data were published in Park, et al.,[17] where it was noted that these patients are sisters. Therefore, whether or not these findings can be generalized to other patients with FPL is unclear. According to the table above, although there were some modest improvements, glycemic control was not substantially achieved until Month 24 (Patient 90112; note that this patient was worsening again by Month 30) or Month 30 (Patient 90117). In addition, insulin was started at Month 24 in both patients, approximately six months before metreleptin was temporarily withdrawn. Therefore, the pre-withdrawal improvements in HbA1c were confounded and difficult to definitively attribute to metreleptin. See below for continued changes in HbA1c over time:

Table 21. HbA1c (%) Over Time[1]; Patients 90112 and 90117

Patient	Baseline	Month 4	Month 8	Month 12	Month 24	Month 36	Month 48	Month 60	Month 72	Month 84
90112	9	8.5	7.8	8.4	6.9	8.7	7.4	7.2	7.5	6.7
90117	9.7	8.6	8.8	9.3	8	7.8	8.5	9.6	10.9	

[1] Note that Month 30 from the above table is missing in this table generated from datasets

Source: Reviewer-generated from BLA datasets (Clinical Efficacy Update, dlabs-2.xpt)

- Patient 90144 initiated metreleptin at the age of 10 years. At the time of enrollment, she was diagnosed as having APL; however, as her disorder progressed the patient's loss of body fat was assessed by the investigator to be more consistent with AGL. By report, she was initiated on treatment based on significant insulin resistance, hypertension, hypertriglyceridemia, and elevated transaminases and evidence of hepatic steatosis on ultrasound. Baseline HbA1c was 4.6%, FPG 74 mg/dL, TG 108 mg/dL, ALT 90 U/L, and AST 48 U/L. After two years of metreleptin treatment (the patient was 12 years of age), she discontinued treatment due to lack of changes in physical appearance. Metabolic parameters had generally remained stable on metreleptin treatment (i.e., no increase from baseline). Following the Year 2 visit, the patient discontinued metreleptin treatment and did not return to the NIH for nine months. At this visit, the patient's metabolic deterioration was evident including development of overt diabetes (HbA1c 7.5%, FPG 232 mg/dL), severe hypertriglyceridemia (622 mg/dL), increased ALT (229 U/L) and AST (91 U/L), elevated urine protein:creatinine ratio (previously normal), and lack of pubertal progression. The patient re-initiated metreleptin treatment and six months after re-starting metreleptin (i.e, the first follow up visit), metabolic abnormalities had improved (HbA1c 4.8%, FPG 85 mg/dL, TG 96 mg/dL, ALT 61 U/L, AST 18 U/L), and the patient also had significant pubertal progression to Tanner stage IV. The NIH investigators noted that the patient's dramatic worsening while off metreleptin may have been exaggerated by the physiologic insulin resistance of puberty, as she was mid-pubertal during that time.

Reviewer comment: The narrative (as well as the publication regarding this patient's stopping and restarting metreleptin therapy[23]) did not mention that she was also started on insulin upon restarting metreleptin; see Table 22. In addition, the confounding of puberty makes this case difficult to interpret.

Table 22. Changes in HbA1c and Diabetes Medications Over Time, NIH Patient 90144

Visit	Baseline	Month 8	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 42 (follow-up?)
Study Day	-1	178	371	535	604	863	1064	1218	1274
HbA1c (%)	4.6	4.5	4.8	5	5.3	7.5	4.8	5.2	4.9
Insulin (µIU/mL)	57.6			114		200	40.5	51.8	49.5
Glucose (mg/dL)	80	94	85	93	108	235	86	94	92
Diabetes medications		Started on metformin 250 mg QD study day 179; increased to 500 mg BID study day 247	Metformin increased to 1000 mg BID on day 372	Metformin 1000 mg BID	Metformin 1000 mg BID	Metformin 1000 mg BID + Insulin sliding scale started	Metformin 1000 mg BID + Insulin sliding scale	Metformin 1000 mg BID (Insulin sliding scale stopped)	Metformin 1000 mg BID
Metreleptin	Start (day 1)	Continue	Continue	Continue	Stop	Restart	Continue	Continue	Continue

Source: Reviewer generated table; datasets: NIH20010769 dconme-2.xpt and NIH20010769 dlabs-2.xpt

Concomitant Medications

Because any alterations in background therapies to treat the metabolic complications of lipodystrophy could confound the efficacy results, the efficacy of metreleptin by concomitant medication was analyzed; analyses were focused on the first 12 months of treatment.

Reviewer comment: Note that metreleptin for lipodystrophy originally obtained fast-track designation (2001) as a result of demonstration of reduction or discontinuation of anti-hyperglycemic medications seen in very preliminary data from NIH trial 991265 (as described in reference 22). Therefore, the capture and reporting of concomitant medications is considered critical to assess the efficacy of metreleptin therapy.

Diabetes Medications

According to the NIH protocol, once patients are enrolled in the trial, other forms of glucose-lowering therapy are not to be increased for at least the first four months. Patients are to be maintained on a stable regimen for six to eight weeks prior to enrollment. Study physicians are to use their best clinical judgment to decrease the dose or frequency of these medications if hypoglycemia occurs. In the absence of hypoglycemia, physicians are to maintain patients on stable glucose-lowering therapies so that the only variable will be increasing dose of metreleptin.

In the NIH trials, 88% of patients were receiving at least one anti-hyperglycemic medication at baseline.

Table 23. Proportion of Patients Receiving Baseline Diabetes Concomitant Medications (NIH Trials)

	All Patients N=72
Receiving Diabetes Medication at Baseline	63 (87.5)
Insulin alone	14 (19.4)
Insulin + metformin	18 (25.0)
Insulin + TZD	2 (2.8)
Metformin alone	14 (19.4)
TZD alone	3 (4.2)
≥ 2 oral agents	12 (16.7)

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 17

Given the 12-month data cut was the primary analysis for the key efficacy assessments outlined in previous sections, the sponsor conducted concomitant diabetes medication analyses focused on the initial 12 months of treatment.

At each analysis time point, patients were classified as to whether their diabetes medications had:

- Stopped (no diabetes medications being taken)
- Decreased (total daily dose decreased but at least one diabetes medication was still being taken)
- Remained Stable (total daily dose was unchanged)
- Increased (total daily dose increased)
- Insulin Added (total daily dose of oral agent(s) was unchanged but insulin added as a new medication)
- Oral Agent Added (total daily dose of baseline insulin and/or oral agents was unchanged but an oral agent added as a new medication)
- Indeterminate (e.g., total daily dose at baseline or at analysis time point could not be determined; or a change in oral diabetes medications (such as metformin stopped while pioglitazone started); or insulin daily dose decreased but oral agent daily dose increased)

Additionally, patients not taking diabetes medications at baseline were classified into the following categories, based on medications being taken at the analysis time point:

- Continued to not take diabetes medications

- Started taking insulin

- Started taking an oral agent

The sponsor also conducted a summary of efficacy according to certain medication subgroups at the Month 4 and Month 12 time points.

Table 24. Change from Baseline to Month 4 and Month 12 by Diabetes Medication Category: Patients with 4 and 12 Month Exposure and Who Received Diabetes Medications at Baseline and/or Month 4 and 12 (NIH Trials)[†††††]

Baseline Medication Category	N	Discontinued	Decreased	Unchanged	Increased	Insulin Added	Oral Added	Indeterminate
On DM Meds at BL								
Month 4								
1 Oral Agent Only	16	2 (12.5)	-	14 (87.5)	-	-	-	-
2 or More Oral Agents	12	2 (16.7)	3 (25.0)	7 (58.3)	-	-	-	-
Insulin Alone	13	2 (15.4)	3 (23.1)	5 (38.5)	1 (7.7)	-	-	2 (15.4)
Insulin + Oral Agent [1]	19	2 (10.5)	4 (21.1)	8 (42.1)	2 (10.5)	-	-	3 (15.8)
Total	**60**	**8 (13.3)**	**10 (16.7)**	**34 (56.7)**	**3 (5.0)**	**0 (0.0)**	**0 (0.0)**	**5 (8.3)**
Month 12								
1 Oral Agent Only	15	2 (13.3)	1 (6.7)	10 (66.7)	-	1 (6.7)	-	1 (6.7)
2 or More Oral Agents	12	3 (25.0)	2 (16.7)	2 (16.7)	1 (8.3)	1 (8.3)	2 (16.7)	1 (8.3)
Insulin Alone	8	4 (50.0)	1 (12.5)	2 (25.0)	-	-	-	1 (12.5)
Insulin + Oral Agent [1]	18	4 (22.2)	6 (33.3)	2 (11.1)	2 (11.1)	-	-	4 (22.2)
Total	**53**	**13 (24.5)**	**10 (18.9)**	**16 (30.2)**	**3 (5.7)**	**2 (3.7)**	**2 (3.7)**	**7 (13.2)**
Not on DM Meds at BL								
Month 4	**2**					-	**2 (100.0)**	-
Month 12	**2**					-	**2 (100.0)**	-

[1] For the category Insulin + Oral Agent, the change from baseline is determined by insulin dose only. It should be noted that all patients in this category were only on 1 oral agent.

Source: Clinical Efficacy Update Table 24

Reviewer comment: I was unable to reproduce this table. The per patient medication data available for review was provided in a separate submission upon request, and at least one discrepancy was noted between the analyses provided in the Clinical Efficacy Update and results from the per patient data (by my assessment, a patient who was considered "unchanged" should have been considered "oral added"). Despite some challenges, I have attempted to determine the individual patients who make up the Month 12 findings. Of the 53 patients who were on anti-hyperglycemic medications at baseline and had 12 month data, 33 patients had generalized lipodystrophy (note that 48 generalized lipodystrophy patients were enrolled overall) and 20 patients had partial lipodystrophy (note that 24 partial lipodystrophy patients were enrolled overall).

[†††††] Potential protocol violations: 3 patients on anti-hyperglycemic medications at baseline who had doses increased by Month 4; 2 patients not on diabetes medications at baseline started on new medications by Month 4

According to my manual review of the medication data:

- ***Of the 13 patients who <u>discontinued</u> anti-hyperglycemic medications by Month 12, 12 had generalized lipodystrophy and one had partial lipodystrophy***
- ***Of the 10 patients who had their dose(s) <u>decreased</u> by Month 12, five patients had generalized lipodystrophy and five had partial lipodystrophy***
- ***Of the 15 patients whose doses were <u>unchanged</u>, 10 patients had generalized lipodystrophy and five had partial lipodystrophy***
- ***Of the three patients who had doses <u>increased</u>,‡‡‡‡‡ one patient had generalized lipodystrophy and two had partial lipodystrophy***
- ***Of the five patients who had <u>oral anti-hyperglycemic medications added</u>,‡‡‡‡‡ two had generalized lipodystrophy and three had partial lipodystrophy***
- ***Of the two patients who had <u>insulin added</u>,‡‡‡‡‡ both had partial lipodystrophy***
- ***Of the seven patients in the <u>indeterminate</u> category,‡‡‡‡‡ four had generalized lipodystrophy and three had partial lipodystrophy***

Descriptive analyses of changes in total daily insulin dose at Months 4 and 12 were also conducted; see table below.

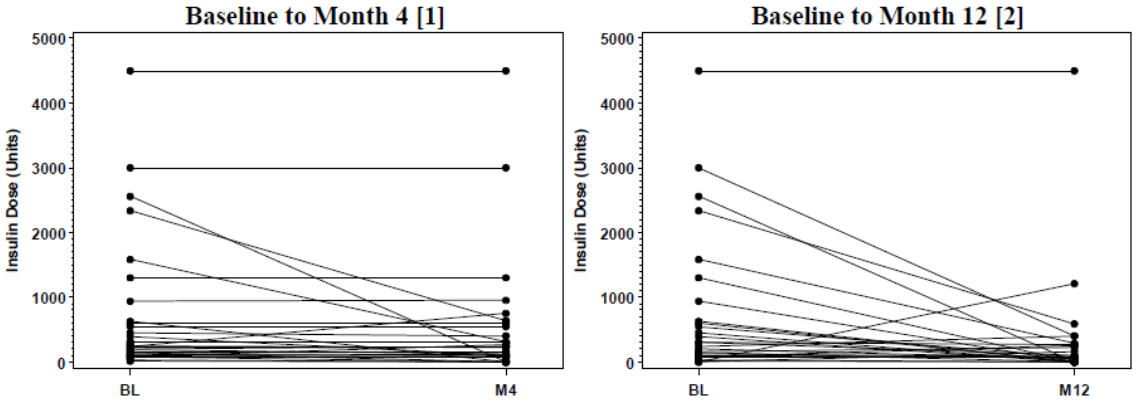
‡‡‡‡‡ The sponsor reports that doses were generally held stable during the first year, except when decreases were necessary to avoid hypoglycemia; however, this was not the case for 14% of patients; in addition, those 10% in the indeterminate category may have had medication changes in the first year in order to optimize glycemic management.

Table 25. Total Daily Insulin Dose at Baseline, Month 4, and Month 12: Patients Who Received Insulin (NIH; ITT Population Observed Data)

	Baseline [1]	**Month 4 [2]**
Received Insulin at Baseline or Month 4 (n)	30	
Mean daily insulin dose (U)	724.1	519.0
Median daily insulin dose (U)	272.5	240.0
Min, Max	12.0, 4500.0	0.0, 4500.0
	Baseline [1]	**Month 12**
Received Insulin at Baseline or Month 12 (n)	26	
Mean daily insulin dose (U)	790.5	335.6
Median daily insulin dose (U)	300.0	74.5
Min, Max	0.0, 4500.0	0.0, 4500.0
[1] 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. [2] Two of the 32 patients identified in Table 24 receiving insulin alone or an insulin + oral agent at Month 4 had doses assessed as indeterminate and therefore not included in this table.		
Source: Clinical Efficacy Update Table 25		

Total daily insulin doses for individual patients from baseline to Month 4 and from baseline to Month 12 are shown in Figure 13.

Figure 13. Individual Total Daily Insulin Dose at Baseline, Month 4, and Month 12: Patients Who Received Insulin (NIH; ITT Population Observed Data)



[1] N = 30 for Month 4. Two of the 32 patients identified in Table 24 receiving insulin alone or an insulin + oral agent at Month 4 had doses assessed as indeterminate and therefore not included in this figure.
[2] N = 26 for Month 12.
Source: Clinical Efficacy Update Figure 18

Specific findings regarding individual patients include the following:

- One patient (90132, 18-year-old female with APL) had a notable increase in insulin dose at Month 12. The patient was not on insulin at baseline and had insulin added at Month 12.[§§§§§]

- Five patients had marked reductions (greater than 1000 U/day) in insulin dose.[******]

- Patient 90122 (14-year-old female with CGL) was on a very high dose of insulin for three years prior to entry in the study (4500 U/day). This patient's insulin doses remained stable through Month 12 of metreleptin treatment, while HbA1c improved from a baseline of 13.7% to 9.2%. The insulin dose was reduced to 3000 U/day after about 16 months of treatment, and reduced even further to 175 U/day after about 2 years of treatment. Despite these reductions in insulin dose, the patient's HbA1c continued to decrease. The patient's HbA1c was 8.2% and 5.6% at Month 21 and Month 36, respectively.

Reviewer comment: It is notable that it took this patient three years to achieve glycemic control. While metreleptin may have played a role in the improvement, it is not clear if additional interventions may have contributed to the observed changes over time.

Lipid Medications

Similar to the diabetes medications analyses, the sponsor conducted concomitant lipid medication analyses focused on the initial 12 months of treatment. During the first 12 months of the NIH trials, concomitant lipid medications were generally held stable per protocol.

In the NIH trials, 50% of patients were receiving at least one lipid-lowering medication at baseline.

[§§§§§] The HbA1c and FPG of Patient 90132 went from 6.3% and 243 mg/dL at baseline, respectively, to 5.7% and 135 mg/dL (Month 4), 6.7% and 270 mg/dL (Month 8), and 6% and 57 mg/dL (Month 12).
[******] One of these patients (90163) was actually reported in the data listings to have started insulin (3000 U total daily dose) on the first day on metreleptin therapy. It is unclear if she was on insulin prior to starting the trial, but if so, it was not reported.

Table 26. Proportion of Patients Receiving Baseline Lipid-Lowering Concomitant Medications (NIH; ITT Population)

	All Patients N=72
Receiving Lipid Medication at Baseline	**36 (50.0)**
Monotherapy	**26 (36.1)**
Fibrate	17 (23.6)
Statin	3 (4.2)
Fish Oil	6 (8.3)
≥ 2 Medications	**9 (12.5)**
Fibrate + Statin	5 (6.9)
Fibrate + Fish Oil	2 (2.8)
Statin + Fish Oil	1 (1.4)
Fibrate + Statin + Fish Oil	1 (1.4)
Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 20	

During the NIH trials, the majority of patients maintained their lipid-lowering medication regimen from baseline to Month 4 (88%) and from baseline to Month 12 (72%). Fibrates are commonly-used medications to treat hypertriglyceridemia (the primary lipid abnormality in patients with lipodystrophy); therefore, the sponsor's analyses focused on changes in fibrate dose.

Table 27. Change from Baseline to Month 4 and Month 12 by Lipid-Lowering Category: Patients with 4 and 12 Month Exposure and Who Received Lipid-Lowering Medications at Baseline and/or Month 4 and 12 (NIH; ITT Population Observed Data)

Baseline Medication Category	N	Stopped	Decreased	Unchanged	Increased	Fibrate Added	Non-Fibrate Added	Indeterminate
On Lipid-Lowering Meds at BL								
Month 4								
Fibrate Alone	16	1 (6.3)	-	15 (93.8)	-	-	-	-
Fibrate Combo [1]	8	-	-	7 (87.5)	-	-	-	1 (12.5)
Non-Fibrate	9	-	1 (11.1)	7 (77.8)	-	1 (11.1)	-	-
Total	**33**	**1 (3.0)**	**1 (3.0)**	**29 (87.9)**	**0 (0.0)**	**1 (3.0)**	**0 (0.0)**	**1 (3.0)**
Month 12								
Fibrate Alone	15	2 (13.3)	-	13 (86.7)	-	-	-	-
Fibrate Combo [1]	6	-	2 (33.3)	3 (50.0)	1 (16.7)	-	-	-
Non-Fibrate	8	-	1 (12.5)	5 (62.5)		2 (25.0)	-	-
Total	**29**	**2 (6.9)**	**3 (10.3)**	**21 (72.4)**	**1 (3.4)**	**2 (6.9)**	**0 (0.0)**	-
Not Lipid-Lowering Meds at BL								
Month 4	1					-	1 (100.0)	-
Month 12	2					2 (100.0)	-	-

[1] The change from baseline is determined by the fibrate dose only.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 26

Reviewer comment: I was unable to reproduce this table. Key findings at Month 12 that I was able to identify (by manual review) include:

- ***The two patients who <u>stopped</u> treatment with fibrate both had generalized lipodystrophy***
- ***The patient whose <u>dose of fibrate was increased</u> had partial lipodystrophy***
- ***All five patients who had a <u>lipid-lowering drug added</u> (fibrate or non-fibrate) had partial lipodystrophy***

At Months 4 and 12, the mean fibrate dose decreased, while the median dose remained constant.

Table 28. Total Daily Fibrate Dose at Baseline, Month 4, and Month 12: Patients Who Received Fibrates (NIH; ITT Population Observed Data)

	Baseline [1]	**Month 4**
Received Fibrate at Baseline or Month 4 (n)	25	
Mean daily fibrate dose (mg)	375.3	341.7
Median daily fibrate dose (mg)	145.0	145.0
Min, Max	0.0, 2400.0	0.0, 2400.0
	Baseline [1]	**Month 12**
Received Fibrate at Baseline or Month 12 (n)	25	
Mean daily fibrate dose (mg)	355.1	220.6
Median daily fibrate dose (mg)	145.0	145.0
Min, Max	0.0, 2400.0	0.0, 2400.0
[1] 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.		
Source: Clinical Efficacy Update Table 27		

Trial FHA101

As the majority of patients in this trial up to the 2012 data cutoff had partial lipodystrophy, the sponsor summarized the patients with generalized lipodystrophy separately, and by individual patient.

Table 29. Individual Efficacy Data: Patients With Generalized Lipodystrophy, FHA101

Patient Number	Visit	HbA1c (%)	FPG (mg/dL)	TG (mg/dL)	ALT (U/L)	AST (U/L)
648001	Baseline	9.1	262	10,623	27	20
	Month 12	7.8	133	140	34	19
648016	Baseline	5.5	110	354	419	208
	Month 12	4.7	77	30	25	35
648022	Baseline	10.2	420	1,845	259	145
	Month 6 [1]	4.5	78	502	19	20
649001	Baseline	9.9	188	554	21	24
	Month 1 [1]	9	161	320	18	27
677002	Baseline	8.4	274	170	51	47
	Month 6 [1]	11.5	239	341	58	51

[1] Last available post-baseline value.
[2] Patient 677002 was withdrawn from the protocol (investigator decision, FHA101 Appendix 3.1) due to family conflict, personal issues, missed appointments and intermittent noncompliance

Source: Clinical Efficacy Update, Table 37

Reviewer comment: Contrast the information in the above table with the data presented below for Patient 648001. Although the following data are from the immunogenicity report in the BLA (note that no leptin neutralizing activity was reported), the change in efficacy over time in this patient was noted that is not included in the table above. There were reportedly compliance issues in this patient after Month 18, although interestingly, reported leptin concentrations do not reflect that.

Table 30. Metabolic Parameters Over the Time of Metreleptin Treatment: Patient 648001 (9 yo F AGL)

Visit	Baseline	Mo 3	Mo 6	Mo 12	Mo 15	Mo 20	Mo 24	Mo 27	Mo 32	Mo 35
Leptin (ng/mL)	0.7	0.7	0.7	1.6	0.7	26.3	25.2	41.3	4.4	8.9
TG (mg/dL)	10623	1059	3901	140	123	392	10851	2036	590	2452
Glucose (mg/dL)	262	277	273	133	155	87	220	163	128	131
HbA1c (%)	9.1	8.4	9.2	7.8	7.2	8.7	9.8	9.7	9.0	9.1

Source: Clinical Addendum, FHA101, Appendix 5.3.2; FHA101 datasets, DCLINLAB

Two of the patients without 12-month data discontinued prematurely: Patient 649001, a 67-year-old female with AGL died from adenocarcinoma, and Patient 677002, a 25-year-old female with CGL was withdrawn from the protocol due to family conflict, personal issues, missed appointments, and intermittent noncompliance. Patient 648022, a 16-year-old female with AGL, had markedly elevated HbA1c and TG at baseline, and demonstrated improvement by Month 6, which was last available post-baseline visit, see Table 29 above. Of note, these changes occurred despite discontinuing insulin and pioglitazone.

By contrast, the results in patients with partial lipodystrophy were modest, which supports this finding in the NIH trials.

Table 31. Change From Baseline to Month 12 in HbA1c, FPG, and Fasting TG: Patients With Partial Lipodystrophy, FHA101

Parameter	Statistic [1][2][3]	Month 3	Month 6	Month 9	Month 12
HbA1c (%)	**N**	19	14	15	8
	Baseline Mean (SD)	7.9 (1.6)	7.7 (1.5)	8.0 (1.7)	8.7 (1.7)
	Change from Baseline				
	Mean (SE)	-0.2 (0.3)	-0.2 (0.4)	-0.3 (0.4)	-0.9 (0.6)
	Median	0.0	-0.1	-0.1	-0.1
	Min, Max	-4.5, 1.2	-4.9, 2.6	-4.8, 3.3	-4.7, 0.4
	95% CI	-0.8, 0.4	-1.2, 0.7	-1.2, 0.6	-2.3, 0.6
FPG (mg/dL)	**N**	18	14	14	8
	Baseline Mean (SD)	138.9 (51.3)	146.4 (53.1)	141.9 (51.5)	172.9 (49.5)
	Change from Baseline				
	Mean (SE)	24.4 (25.0)	-26.4 (13.8)	7.4 (23.2)	-42.0 (22.4)
	Median	-1.0	-25.5	6.5	-33.5
	Min, Max	-140, 325	-144, 74	-143, 175	-127, 43
	95% CI	-28, 77	-56, 3	-43, 58	-95, 11
Fasting TG (mg/dL)	**N**	18	14	14	8
	Baseline Mean (SD)	310.3 (298.2)	333.3 (336.5)	292.0 (291.5)	338.8 (255.0)
	Baseline Median	251.0	227.0	227.0	322.5
	Change from Baseline				
	Mean (SE)	-37.8 (63.6)	-60.9 (63.2)	-19.4 (71.8)	-119.8 (84.1)
	Median	-16.5	-11.5	3.0	-81.0
	Min, Max	-807, 388	-844, 130	-772, 519	-644, 129
	Percent Change from Baseline				
	Mean (SE)	12.3 (18.1)	5.1 (13.3)	31.2 (35.8)	-23.1 (15.0)
	Median	-9.8	-4.4	1.5	-32.4
	Min, Max	-65, 193	-68, 120	-62, 481	-70, 39
	95% CI	-25.9, 50.6	-23.5, 33.7	-46.1, 108.5	-58.5, 12.4

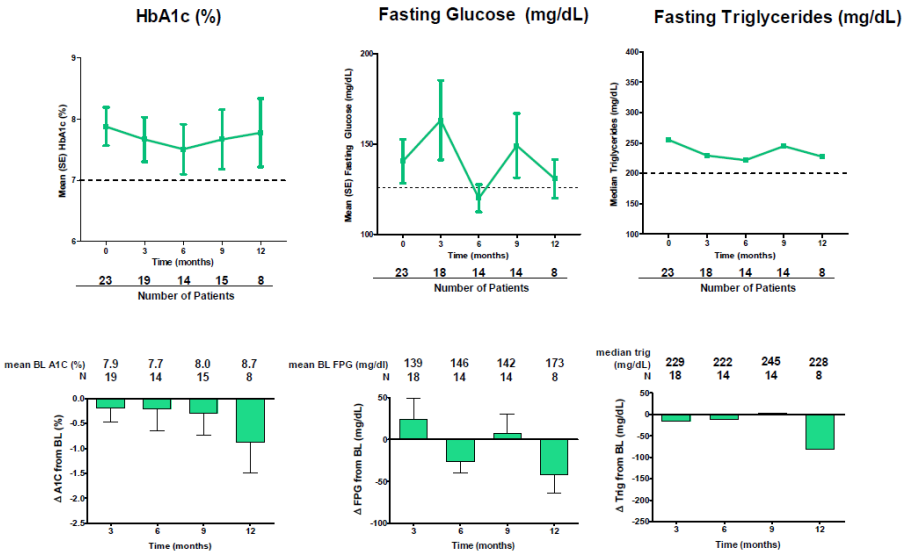
[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time 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] 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, Table 38

Figure 14. Key Efficacy Parameters over Time and by Change From Baseline to Month 3, 6, 9, and 12: Patients with Partial Lipodystrophy; FHA101



[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.

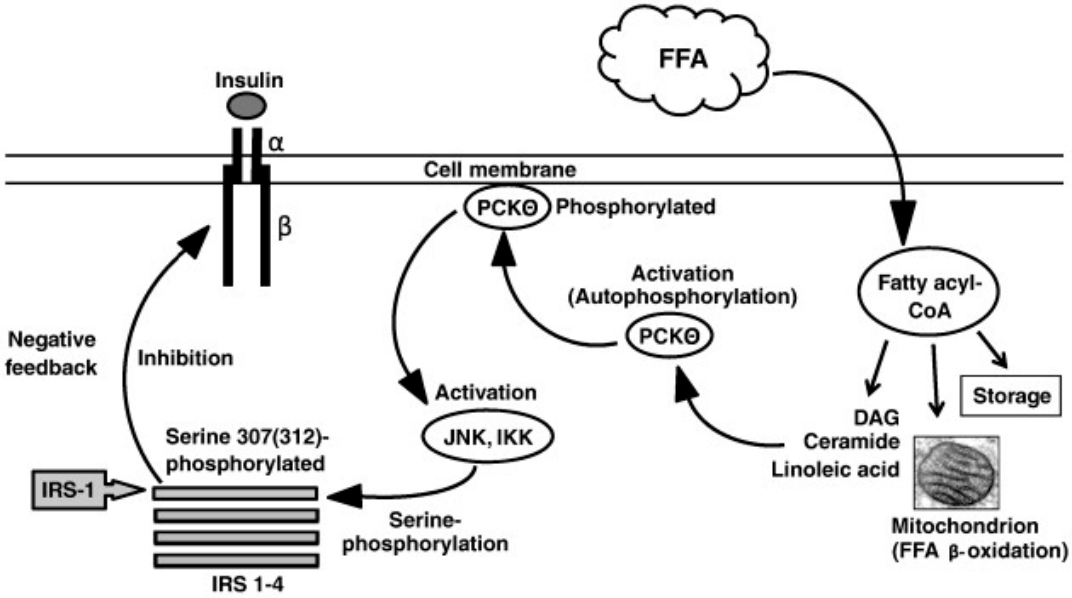
Source: Clinical Efficacy Update, Figure 26

Reviewer comment: There are very limited data at the 12-month time point (n = 8); therefore results at Month 12 should be interpreted with caution. Note that the patients with Month 12 data have the highest mean baseline HbA1c and fasting glucose.

6.1.5 Analysis of Secondary Endpoints

Given the research orientation of these trials, no endpoints were formally considered "secondary"; however, additional endpoints of interest from the NIH trials are presented in this section. Some of these endpoint assessments, for example, circulating free fatty acids (FFAs) and measures of insulin resistance, describe and refine the potential mechanisms whereby patients with lipodystrophy develop co-morbid conditions and how leptin may affect the disease. In lipodystrophy, in which storage of triglycerides is disrupted, circulating FFAs become pathogenic. In the following figure from Capurso[24], the mechanism by which excess FFAs (in this case, in the metabolic syndrome) leads to insulin resistance is described. The authors note that when fatty acid flux exceeds the capacity of oxidation or storage, fatty acids and intermediates of fatty acid metabolism accumulate and dysregulate insulin signaling by serine phosphorylation of insulin receptor substrate (IRS)-1.

Figure 15. Role of Free Fatty Acids in Insulin Receptor Signaling



Source: Reference 24

The results for completed NIH trial 991265 and ongoing trial 20010769 based on an earlier data cut (31 Jul 2009) were presented in the original BLA submission in December 2010. The sponsor provided an Efficacy Update with data based on a more recent data cut (July 2011) that includes more limited efficacy data.

While the following endpoint data were collected at the study site for all patients, some of the data are available for 29 patients from the 2005 data cut only and therefore, where applicable, the analyses were conducted for this subpopulation.

Reviewer comment: Given that the population, metabolic abnormalities, and response to therapy could be different for the first 29 patients versus the entire 72 patient population, these results should be interpreted with caution.

The original study report for the NIH trials includes the following secondary endpoints:

- Fasting lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and free fatty acids)
- Fasting insulin
- Glucose, insulin, and free fatty acid profiles from the OGTT
- Glucose profiles from the insulin tolerance test
- Glucose and insulin profiles from the IVGTT
- The usage of diabetes and lipid medications
- Resting metabolic rate

- Hepatic: liver volume, ALT, AST, liver biopsy results where available
- Endocrine
    - Hypothalamic-pituitary-gonadal axis: LH, FSH, estradiol, testosterone
    - Hypothalamic-pituitary-thyroid axis: TSH, T3, T4
    - Hypothalamic-pituitary-adrenal axis: cortisol, ACTH
- Anthropometric measures

Other Lipids

Mean LDL-C was mildly elevated at baseline (118 mg/dL) with a mean decrease of 17 mg/dL at Month 4 and 28 mg/dL at Month 12. Mean HDL-C was low at baseline (32 mg/dL) and there were small mean decreases (-1.2 mg/dL at Month 4 and -0.7 at Month 12). Some of the reduction in total cholesterol was thought to be due to the decrease in TG concentrations following metreleptin treatment since TG-rich particles, such as very low density lipoprotein (VLDL) particles, also contain cholesterol.

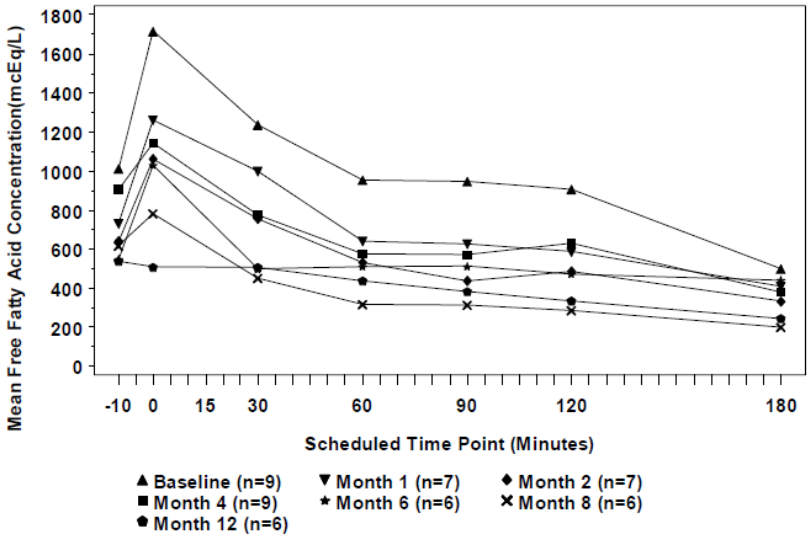
Table 32. Mean (SE) Change from Baseline to Month 12 in Fasting Lipids, NIH Trials

Parameter	Statistic[1][2][3]	Month 4	Month 8	Month 12
Free Fatty Acids (mcEq/L)	**N**	35	39	36
	Baseline mean (SD)	804.7 (685.7)	767.0 (685.1)	719.6 (699.8)
	Change from baseline			
	Mean (SE)	-358.7 (114.9)	-247.1 (107.1)	-252.9 (117.9)
	Median	-159.00	-104.00	-151.50
	Min, Max	-2959.0, 828.0	-2725.0, 957.0	-2596.0, 1514.0
	95% CI	-592.2, -125.2	-463.9, -30.2	-492.32, -13.57
LDL Cholesterol (mg/dL)	**N**	30	33	32
	Baseline mean (SD)	117.9 (49.1)	109.2 (55.5)	116.8 (49.4)
	Change from baseline			
	Mean (SE)	-17.3 (8.7)	-26.1 (7.7)	-27.6 (8.1)
	Median	-7.00	-19.00	-18.00
	Min, Max	-158.0, 105.0	-176.0, 45.0	-168.0, 54.0
	95% CI	-35.0, 0.4	-41.8, -10.4	-44.2, -11.0
HDL Cholesterol (mg/dL)	**N**	44	50	50
	Baseline mean (SD)	32.0 (9.9)	30.7 (9.4)	31.6 (9.0)
	Change from baseline			
	Mean (SE)	-1.16 (0.9)	-0.20 (1.0)	-0.72 (1.0)
	Median	-1.00	-1.50	-1.00
	Min, Max	-12.0, 14.0	-18.0, 17.0	-19.0, 16.0
	95% CI	-2.9, 0.6	-2.3, 1.9	-2.7, 1.2
Total Cholesterol (mg/dL)	**N**	46	53	52
	Baseline mean (SD)	240.4 (124.0)	235.6 (156.03)	235.9 (124.8)
	Change from baseline			
	Mean (SE)	-70.54 (18.0)	-64.6 (17.8)	-67.7 (13.9)
	Median	-47.00	-42.00	-43.00
	Min, Max	-475.0, 312.0	-628.0, 60.0	-531.0, 57.0
	95% CI	-106.8, -34.3	-100.3, -28.9	-95.7, -39.8

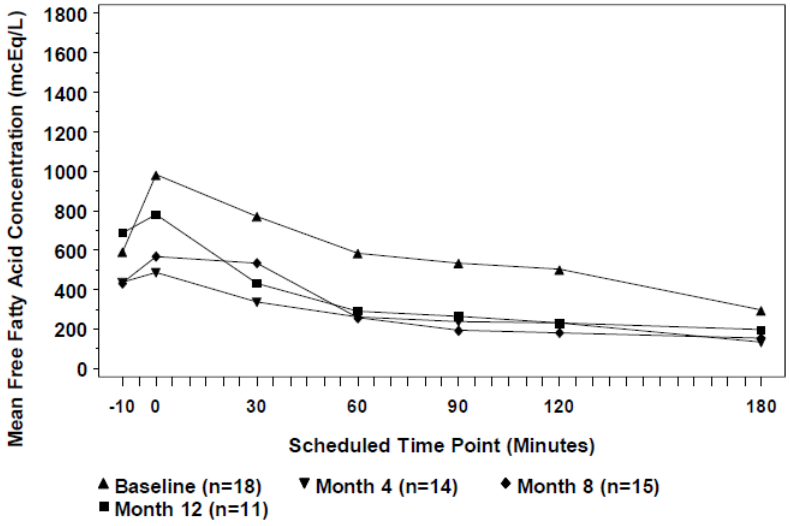
[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time 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.

Source: Clinical Efficacy Update, Table 19

Figure 16. Mean Free Fatty Acid Profile by Visit from the Oral Glucose Tolerance Test; ITT Patients in Study 991265 (Top, N=9) and Study 20010769 (Bottom, N=20), 2005 Datacut



Notes: - Cohort 1 includes subjects who initiated metreleptin treatment in Study 991265.
- Baseline profile is defined as the last available profile before the subject received the first injection of metreleptin.
- Only the visits at which at least 5 subjects had data were displayed.
- Time point 0 refers to the time when oral glucose solution was administered for oral glucose tolerance test.



Notes: - Cohort 2 includes subjects who initiated metreleptin treatment in Study 20010769.
- Baseline profile is defined as the last available profile before the subject received the first injection of metreleptin.
- Only the visits at which at least 10 subjects had data were displayed.
- Time point 0 refers to the time when oral glucose solution was administered for oral glucose tolerance test.

Source: NIH Study Report Body, Supporting Data Summaries 2.6.3.3.1 and 2.6.3.3.2

Insulin Sensitivity

Fasting Insulin

Fasting insulin is a marker of insulin resistance. Fasting insulin data are only available for the 2005 data cut (n = 29). The data are further limited because fasting insulin concentrations were only evaluated in those patients who were not receiving concomitant insulin therapy. Decreases in mean fasting insulin concentrations were observed at Months 4 and 8 of metreleptin treatment and a mean increase was observed at Month 12.

Table 33. Mean Change From Baseline in Fasting Insulin Concentrations in Patients Who Were Not Treated With Insulin During the NIH Trials, 2005 Data Cut (N = 10)

	Statistics	Month 4	Month 8	Month 12
Fasting Insulin(µIU/mL)	**N**	10	8	8
	Baseline Mean (SD)[1]	28.1 (24.6)	27.0 (26.4)	27.0 (26.4)
	Change from Baseline			
	Mean (SE)	-3.0 (4.6)	-8.0 (6.5)	2.9 (4.5)
	Median	-3.9	-3.8	-0.3
	Min, Max	-19.0, 32.5	-48.0, 13.6	-18.6, 22.7

SD = standard deviation; SE = standard error; OGTT = oral glucose tolerance test

[1] 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. If baseline value from insulin test was missing, the baseline fasting insulin value from the OGTT test was used.
Source: NIH Study Report, Table 17

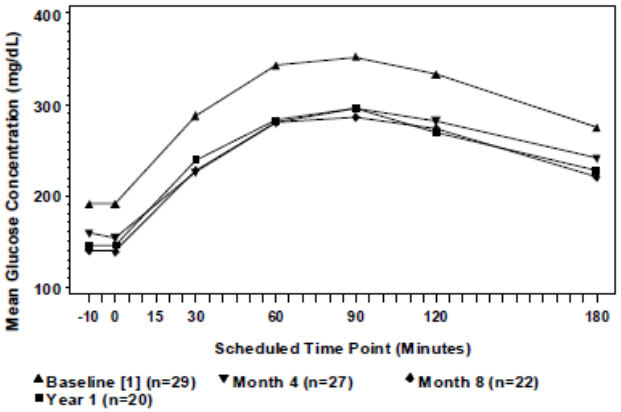
Oral Glucose Tolerance Test

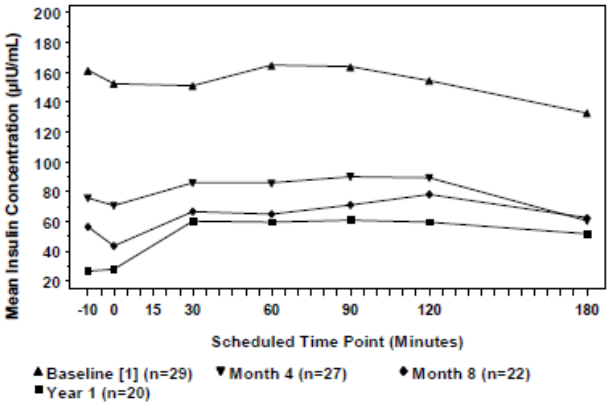
Mean plasma glucose and insulin profiles in response to an oral glucose tolerance test are presented in the figure below for the subpopulation from the 2005 data cut. At baseline, mean fasting plasma glucose values were elevated at close to 200 mg/dL with excursions to the mid-300s after the glucose load.

After four months of metreleptin treatment, both fasting glucose and the response to the glucose load were reduced, and improvements were sustained through Year 1. Corresponding changes from baseline in glucose AUC (0-3 hr) were (mean ± SE): -148.3 ± 49.4 mg*hr/dL at Month 4 and -158.8 ± 68.3 mg*hr/dL at Year 1.

Consistent with the improvement in glucose levels, the corresponding insulin profiles showed similar results, indicating improvement in insulin sensitivity. Corresponding changes from baseline in the insulin AUC (0-3 hr) in the oral glucose tolerance test were (mean ± SE): -234.0 ± 146.5 (µIU*hr/mL) at Month 4 and -408.3 ± 309.7 (µIU*hr/mL) at Year 1.

Figure 17. Mean Glucose and Insulin Profiles by Visit from the Oral Glucose Tolerance Test, 2005 Data Cut (N = 29)



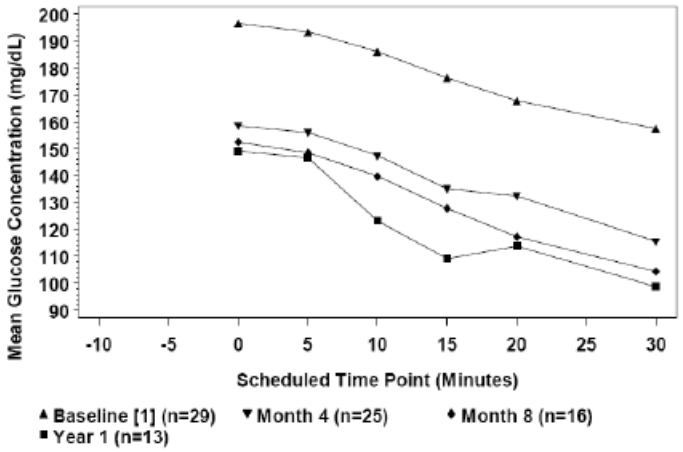


Notes: Baseline profile is defined as the last available profile before the patient received the first injection of metreleptin.
- Only the visits which are common to both cohort 1 and cohort 2 patients, and visits at which at least 12 patients had data were displayed.
- Time point 0 refers to the time when oral glucose solution was administered for the oral glucose tolerance test.
Source: NIH Study Report, Figure 10

Insulin Tolerance Test

Plasma glucose profiles in response to an insulin tolerance test (injection of 0.2 U insulin / kg body weight) are shown in the following figure for the subpopulation from the 2005 data cut. Similar to findings with the oral glucose tolerance test, the mean glucose profile in response to an intravenous insulin challenge was lower after Month 4 of metreleptin treatment, consistent with increased insulin sensitivity, with similar results observed at Month 8 and Year 1 of treatment.

Figure 18. Mean Glucose Profile by Visit from the Insulin Tolerance Test, 2005 Data Cut (N = 29)



Notes: Baseline profile is defined as the last available profile before the patient received the first injection of metreleptin.
- Only the visits which are common to both cohort 1 and cohort 2 patients, and visits at which at least 12 patients had data were displayed.
- Time point 0 refers to the time when regular human insulin was administered intravenously for insulin tolerance test.
Source: NIH Study Report, Figure 11

Resting Metabolic Rate and Body Composition

Resting energy expenditure was measured with indirect calorimetry and was decreased with metreleptin treatment by 134.4 ± 74.6 kcal/24 hr and 253.8 ± 122.3 kcal/24 hr (mean ± SE) at Month 4 (n=16) and Month 12 (n=16), respectively, from a baseline (n=22) of 1732.3 ± 77.9 kcal/24 hr.

Minimal or no changes in mean ± SE body fat as measured by skin fold thicknesses were observed with metreleptin treatment at Month 4 (+0.5 ± 0.7 %) and at Month 12 (+0.0 ± 0.6 %) from a baseline of 19.3 ± 1.4%.

Reviewer comment: The NIH published these data[19] and reported (using dual energy x-ray absorptiometry) that small decreases in fat mass and lean body mass, without change in bone mineral content or density, were seen after four months of metreleptin treatment but with no significant change from four to 12 months of continued treatment. The decrease in resting metabolic rate may reflect decreases in hyperphagia and energy intake.

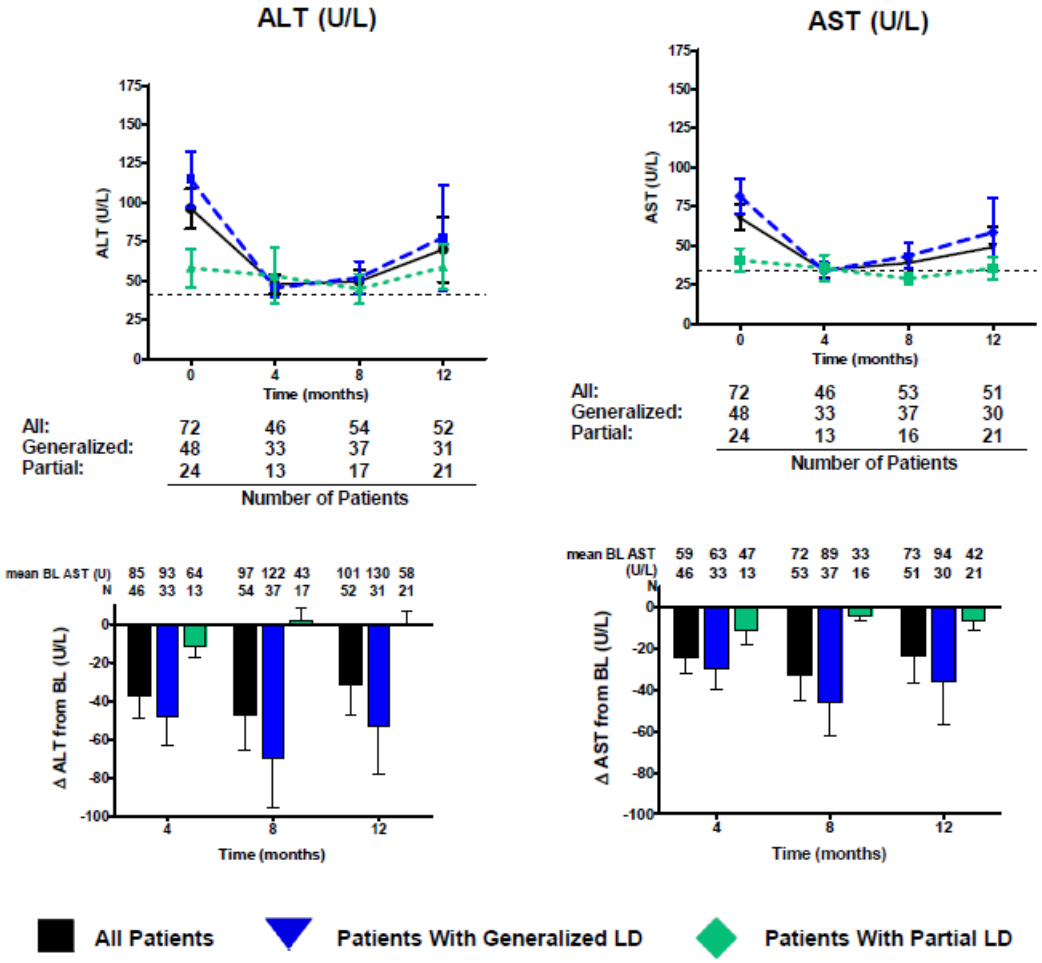
Hepatic Parameters

Given the propensity for patients with lipodystrophy to store fat ectopically, particularly in the liver, non-alcoholic fatty liver disease (NAFLD) is a commonly-described condition associated with this disease. When NAFLD is characterized as non-alcoholic

steatohepatitis (NASH), patients are at risk for developing hepatic fibrosis and cirrhosis, which can progress to liver failure. There are no currently FDA-approved drugs for the treatment of NASH.

The NIH study report included information on the effect on hepatic enzymes and liver volume, the FHA101 study report included limited information on hepatic enzyme changes, and the sponsor's clinical efficacy summary document included hepatic enzymes and liver volume. Limited pathology information (liver biopsies) were reported in two publications.[25,26] Our FDA colleagues in the Division of Gastroenetrology and Inborn Errors Products will be providing context and interpretation of these findings. Below is a summary of ALT and AST changes provided by the sponsor in the BLA.

Figure 19. Mean (SE) ALT and AST Concentrations Over Time and Change from Baseline at Month 4, 8, and 12: All Patients, Generalized Lipodystrophy and Partial Lipodystrophy (ITT Population Observed Data for Each Efficacy Parameter)



[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., ALT and AST) 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 the ULN for ALT (41 U/L) and AST (34 U/L).

Source: Clinical Efficacy Update, Figure 14

Endocrine Parameters

In females, improvements in LHRH-stimulated LH were noted after four months of metreleptin with increased estradiol and decreased testosterone levels. Results from the LHRH stimulation test are available prior to metreleptin in 17 female patients (limited data in one of these) and after four months of metreleptin treatment in 10 female

patients. LH levels increased approximately 4-fold from baseline to the peak value (60 min) in response to LHRH prior to metreleptin treatment. After four months of metreleptin, the LH peak induction was similar (approximately 4-fold) but longer lasting with the peak maintained from 60 to 180 min after LHRH.

Reproductive steroid hormone (serum estradiol and testosterone) levels were also measured at baseline and at 1, 4, 6, and 8 months after metreleptin treatment in patients from the NIH 991265 trial (all female). At baseline, mean ± SE estradiol concentrations were 37.1 ± 12.0 pg/mL, and mean total testosterone concentrations were 84.7 ± 31.4 ng/dL (n = 9). After four months of metreleptin treatment, estradiol increased to 72.5 ± 32.3 pg/mL and mean testosterone levels decreased to 33.6 ± 5.9 ng/dL (n = 8).

No changes in LHRH-stimulated LH occurred after metreleptin in the few males who had this test.

There was no effect of metreleptin treatment on the hypothalamic-pituitary-thyroid axis. Prior to metreleptin therapy, mean TSH increased in response to TRH from 1.6 ± 0.35 mIU/L at -15 min to a peak of 13.1 ± 2.0 mIU/L at 30 min (n = 12). After four months of metreleptin therapy, the TSH response to TRH showed similar results (from mean of 1.4 ± 0.37 mIU/L to a peak of 12.2 ± 1.9 mIU/L at 30 min, n = 8).

In addition, TSH, thyroxine (T4), and triiodothyronine (T3) levels were measured at baseline and during metreleptin treatment in patients from the NIH 991265 trial. Non-stimulated TSH concentrations in these patients were normal at baseline (1.2 ± 0.2 mIU/L, mean ± SE, [n = 9]) and remained stable through Month 4 (1.2 mIU/L ± 0.2, [n = 8]) and Month 8 (1.1 ± 0.2 mIU/L, [n = 8]). Mean (± SE) T3 concentrations (baseline: 115.2 ± 12.3 ng/dL, [n = 9]; Month 4: 111.0 ± 9.4 ng/dL [n = 8]; Month 8: 109.4 ± 10.2 ng/dL [n = 8]), and T4 concentrations (baseline: 10.5 ± 1.0 µg/dL [n = 6], Month 1: 11.3 ± 1.0 µg/dL [n = 4]) also remained stable.

There was no effect of metreleptin treatment on the hypothalamic-pituitary-adrenal axis. In patients from the NIH 991265 trial (n = 7), unstimulated ACTH and cortisol concentrations at baseline were 28.6 ± 4.8 pg/mL and 20.1 ± 4.3 µg/dL, respectively (mean ± SE). After four months of metreleptin treatment, mean ACTH and cortisol concentrations were largely unchanged (30.2 ± 4.6 pg/mL and 17.3 ± 2.2 µg/dL, respectively). In addition, the ACTH and cortisol response to CRH administration was similar before and four months after metreleptin therapy.

A diurnal ACTH and cortisol analysis was completed for patients enrolled directly into the NIH trial 20010769. Mean 8:00 am ACTH and cortisol levels at baseline were 39.1 ± 4.5 pg/mL (n = 13) and 21.8 ± 1.8 µg/dL (n = 19). After four months of metreleptin treatment, 8:00 am ACTH and cortisol levels were slightly lower but similar to baseline (33.9 ± 7.2 pg/mL and 15.3 ± 1.5 µg/dL, respectively, mean ± SE). At baseline,

midnight cortisol levels were low (5.8 ± 0.7 µg/dL, n = 19) as expected based on diurnal variation (and ruling out hypercortisolism) and did not change after four months of metreleptin (5.1 ± 1.1 µg/dL, n = 16).

6.1.6 Other Endpoints

See Section 6.1.5.

6.1.7 Subpopulations

Given the heterogeneity of lipodystrophy phenotypes, it is important to adequately characterize the effect of metreleptin in subpopulations, in order to identify patients who may or may not be likely to achieve benefit. As noted in the protocol description, the inclusion criteria for leptin concentrations at baseline in the NIH trial increased over time. Notably, patients enrolled in the initial trial had large improvements in metabolic endpoints,[22] whereas this effect appears less so in the subsequent trial enrollment. These earlier patients were primarily patients with generalized lipodystrophy, but patients with partial lipodystrophy were enrolled if they had low leptin concentrations.

Overall (and as would be expected), as shown in Table 34, patients with generalized lipodystrophy have a greater response in HbA1c and TG than patients with partial lipodystrophy and patients with lower baseline leptin concentrations have a greater response than patients with higher leptin concentrations.

Table 34. Change From Baseline to Month 12 in Key Efficacy Parameters: Intrinsic Factors (NIH; ITT Patients with Baseline and Month 12 Data)

	Mean (SE) HbA1c (%)			Mean (SE) FPG (mg/dL)			Median TG (mg/dL)			
Intrinsic Factor	**N**	**BL**	**Δ from BL at Month 12**	**N**	**BL**	**Δ from BL at Month 12**	**N**	**BL**	**Δ from BL at Month 12**	**Percent Δ from BL at Month 12**
Overall Population	50	8.2 (0.3)	-1.4 (0.2)	52	169.9 (12.3)	-41.8 (11.7)	51	359.0	-121.0	-44.8
LD Subtype										
CGL	20	9.0 (0.5)	-2.2 (0.4)	22	169.6 (16.3)	-32.3 (21.1)	22	452.0	-284.0	-60.7
AGL	9	8.0 (0.6)	-1.8 (0.4)	9	203.4 (38.2)	-87.6 (23.5)	8	348.0	-211.5	-67.4
FPL	17	7.7 (0.5)	-0.5 (0.3)	17	158.5 (22.8)	-32.5 (14.7)	17	357.0	-74.0	-29.8
APL	4	6.7 (1.4)	-0.1 (0.2)	4	144.3 (35.5)	-30.3 (52.8)	4	334.5	-50.5	-7.3
Gender										
Male	6	7.7 (1.0)	-1.3 (0.7)	7	135.4 (26.4)	-34.3 (18.7)	7	141.0	-40.0	-27.9
Female	44	8.3 (0.3)	-1.4 (0.2)	45	175.2 (13.5)	-42.9 (13.2)	44	427.0	-207.0	-49.6
Age										
≤12 yrs	11	6.1 (0.4)	-0.7 (0.4)	12	113.3 (13.9)	-25.0 (15.2)	12	230.0	-5.5	-5.2
>12 yrs to <18 yrs	14	9.8 (0.5)	-2.3 (0.4)	15	191.3 (26.8)	-35.9 (30.3)	15	433.0	-263.0	-66.1
<18 yrs	25	8.1 (0.5)	-1.6 (0.3)	27	156.7 (17.6)	-31.0 (17.9)	27	322.0	-115.0	-42.1
≥18 yrs	25	8.3 (0.4)	-1.2 (0.3)	25	184.2 (16.9)	-53.3 (14.7)	25	487.0	-300.5	-46.4
Race										
Caucasian	34	8.0 (0.4)	-1.1 (0.2)	35	171.3 (16.3)	-44.3 (12.5)	34	358.0	-110.0	-32.4
Hispanic	4	8.0 (1.5)	-2.4 (1.5)	4	173.3 (54.2)	-80.3 (51.5)	4	518.5	-393.0	-71.0
Black	5	8.4 (0.9)	-1.2 (0.9)	6	159.8 (28.6)	-1.8 (58.1)	6	679.5	-370.0	-47.3
Baseline Metabolic Abnormalities										
HbA1c ≥6%	40	8.9 (0.3)	-1.8 (0.2)	40	192.0 (13.8)	-52.3 (14.3)	39	433.0	-230.0	-54.2
Trig ≥200 mg/dL	36	8.4 (0.4)	-1.4 (0.3)	37	183.6 (15.6)	-45.9 (15.3)	37	503.0	-303.0	-54.2
HbA1c <6% and Trig <200 mg/dL	5	5.1 (0.2)	0.1 (0.2)	6	84.7 (4.8)	-2.2 (5.2)	6	129.5	13.0	10.7
Leptin Levels [1]										
Lower	36	8.3 (0.4)	-1.8 (0.3)	38	176.1 (15.1)	-49.7 (15.1)	38	424.5	-246.5	-55.2
Higher	12	7.7 (0.5)	-0.2 (0.2)	12	141.1 (20.6)	-21.0 (15.4)	12	298.0	-65.0	-24.4

[1] Lower: Male <2.0 ng/mL / Female <4.0 ng/mL; Higher: Male ≥2.0 ng/mL / Female ≥4.0 ng/mL.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Table 23

Reviewer comment: Note that baseline HbA1c and fasting TG values for AGL and FPL are similar, yet patients with AGL seem to have had a better response than patients with FPL. In addition, baseline TG was similar for APL, AGL, and FPL, yet patients with APL had less TG-lowering.

The following table and figures illustrate the differences in metabolic improvements over time by lipodystrophy type (generalized or partial) overall and in those patients with various degrees of baseline abnormalities.

Table 35. Key Efficacy Parameters at Baseline and Month 12 in Generalized and Partial Lipodystrophy: All Patients and Patients with Elevated HbA1c, Fasting Glucose, and TG, NIH Trials

HbA1c (%)	All			Baseline HbA1c ≥6%			Baseline HbA1c ≥7%			Baseline HbA1c ≥8%		
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized LD	29	8.7 (0.4)	-2.0 (0.3)	26	9.1 (0.3)	-2.3 (0.3)	24	9.3 (0.3)	-2.4 (0.3)	19	9.8 (0.3)	-2.7 (0.3)
Partial LD	21	7.5 (0.5)	-0.4 (0.2)	14	8.6 (0.5)	-0.8 (0.3)	11	9.2 (0.5)	-1.0 (0.4)	7	10.1 (0.6)	-1.4 (0.4)
Fasting Glucose (mg/dL)	**All**			**Baseline Glucose ≥126 mg/dL**								
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12						
Generalized LD	31	179.5 (15.9)	-48.3 (16.9)	21	218.6 (17.8)	-82.1 (16.5)						
Partial LD	21	155.8 (19.3)	-32.1 (14.8)	11	220.9 (22.5)	-68.6 (23.2)						
Fasting TG (mg/dL)	**All**			**Baseline TG ≥200 mg/dL**			**Baseline TG ≥350 mg/dL**			**Baseline TG ≥500 mg/dL**		
Median	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized LD	30	414.5	-246.5	21	600.0	-432.0	17	836.0	-692.0	12	1526.5	-1117.0
Partial LD	21	357.0	-74.0	16	430.0	-95.5	11	550.0	-298.0	7	1237.0	-499.0

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.
In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin.

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 3

Reviewer comment: Changes in efficacy parameters are shown in a number of analyses by higher baseline value cutoffs, including the table above (e.g., baseline HbA1c 8% or greater). These data should be interpreted with caution; without a comparator group, the potential for contribution of a regression to the mean the the proported greater improvements in these subgroups cannot be dismissed.

The following table summarizes additional endpoints in patients with generalized versus partial lipodystrophy in the NIH trials.

Table 36. Change From Baseline in Efficacy Parameters for Patients with Generalized and Partial Lipodystrophy, NIH Trials

	Generalized lipodystrophy (N=48)			Partial lipodystrophy (N=24)		
	Month 4	Month 8	Month 12	Month 4	Month 8	Month 12
FFA (mEq/L)	n=24 -249.88	n=24 -199.88	n=22 -158.41	n=11 -596.09	n=15 -322.53	n=14 -401.50
Total cholesterol	n=33 -73.82	n=36 -61.08	n=31 -95.23	n=13 -62.23	n=17 -72.12	n=21 -27.14
LDL-C (mg/dL)	n=24 -21.58	n=26 -31.27	n=21 -34.33	n=6 -0.33	n=7 -6.86	n=11 -14.73
HDL-C (mg/dL)	n=32 -0.63	n=35 -0.34	n=31 -1.10	n=12 -2.58	n=15 0.13	n=19 -0.11
ALT (U/L)	n=33 -47.82	n=37 -69.84	n=31 -52.84	n=13 -11.23	n=17 1.76	n=21 0.29
AST (U/L)	n=33 -29.67	n=37 -45.51	n=30 -35.70	n=13 -11.08	n=16 -2.50	n=21 -6.62
Liver volume (mL)	n=19 -662.76	n=18 -948.58	n=11 -1454.18	n=4 -253.00	n=6 -200.17	n=6 -171.33

Source: Summary of Clinical Efficacy, Supporting Data Summaries 2.16.4 and 2.16.7

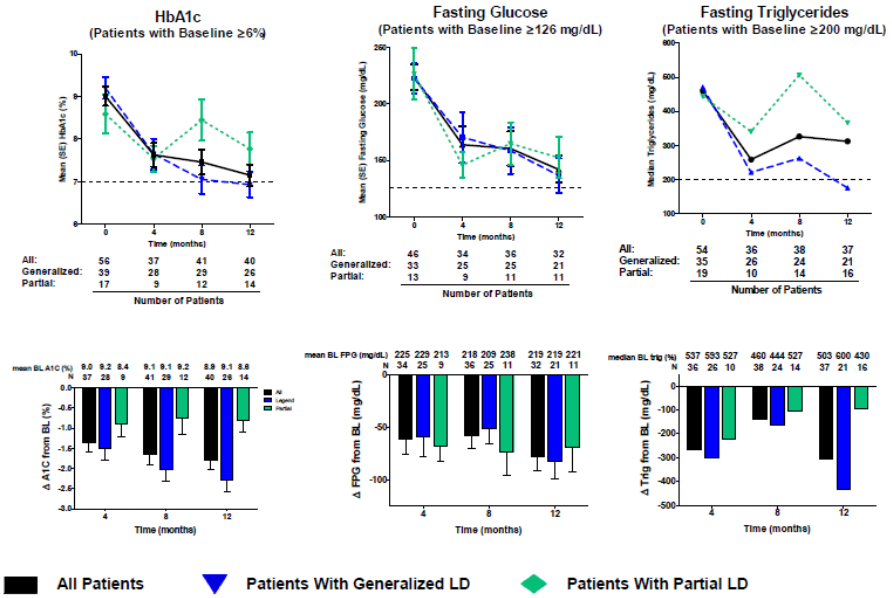
Table 37. Key Efficacy Parameters at Baseline and Month 12 in Generalized and Partial Lipodystrophy: All Patients and Patients with Elevated HbA1c, FPG, and TG, FHA101

HbA1c (%)	All			Baseline HbA1c ≥ 6%			Baseline HbA1c ≥ 7%		
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized	2	7.3 (1.8)	-1.1 (0.3)	1	9.1 (na)	-1.3 (na)	1	9.1 (na)	-1.3 (na)
Partial	8	8.7 (0.6)	-0.9 (0.6)	8	8.7 (0.6)	-0.9 (0.6)	7	9.0 (0.6)	-1.0 (0.7)
Fasting Glucose (mg/dL)	**All**			**Baseline Glucose ≥ 126 mg/dL**					
Mean (SE)	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12			
Generalized	2	186.0 (76.0)	-81.0 (48.0)	1	262.0 (na)	-129.0 (na)			
Partial	8	172.9 (17.5)	-42.0 (22.4)	7	184.4 (15.2)	-49.7 (24.2)			
Fasting TG (mg/dL)	**All**			**Baseline TG ≥ 200 mg/dL**			**Baseline TG ≥ 500 mg/dL**		
Median	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12	n	Baseline	Δ from BL at Month 12
Generalized	2	5488.5	-5403.5	2	5488.5	-5403.5	1	10623.0	-10483.0
Partial	8	322.5	-81.0	5	341.0	-166.0	1	919.0	-644.0

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 4

Reviewer comment: Although the FHA101 trial (Table 37) does not appear to demonstrate the same degree of discrepancy in HbA1c change between generalized and partial lipodystrophy patients as the NIH trials (see Table 35, above), note that in FHA101 the mean baseline HbA1c in the two patients with generalized lipodystrophy who have 12 month data is lower than that of the patients with partial lipodystrophy. Contrast the baseline HbA1c values in FHA101 to those in the NIH trials (i.e., the mean value in the generalized patients in the NIH trials was similar to the mean value in the partial patients in the FHA101 trial and vice versa). This supports the concept that the observed greater improvements in HbA1c in the generalized patients may be partially independent of baseline values. (Although the small sample sizes, lack of a placebo control, and changes in concomitant medications limit the conclusions.) Results in generalized and partial lipodystrophy, overall and by baseline metabolic abnormalities are further explored in figures and tables below.

Figure 20. Key Efficacy Parameters in Patients with Baseline HbA1c 6% or Greater, FPG 126 mg/dL or Greater, or TG 200 mg/dL or Greater: All Patients, Generalized Lipodystrophy, and Partial Lipodystrophy (NIH; Observed Data for Each Efficacy Parameter)

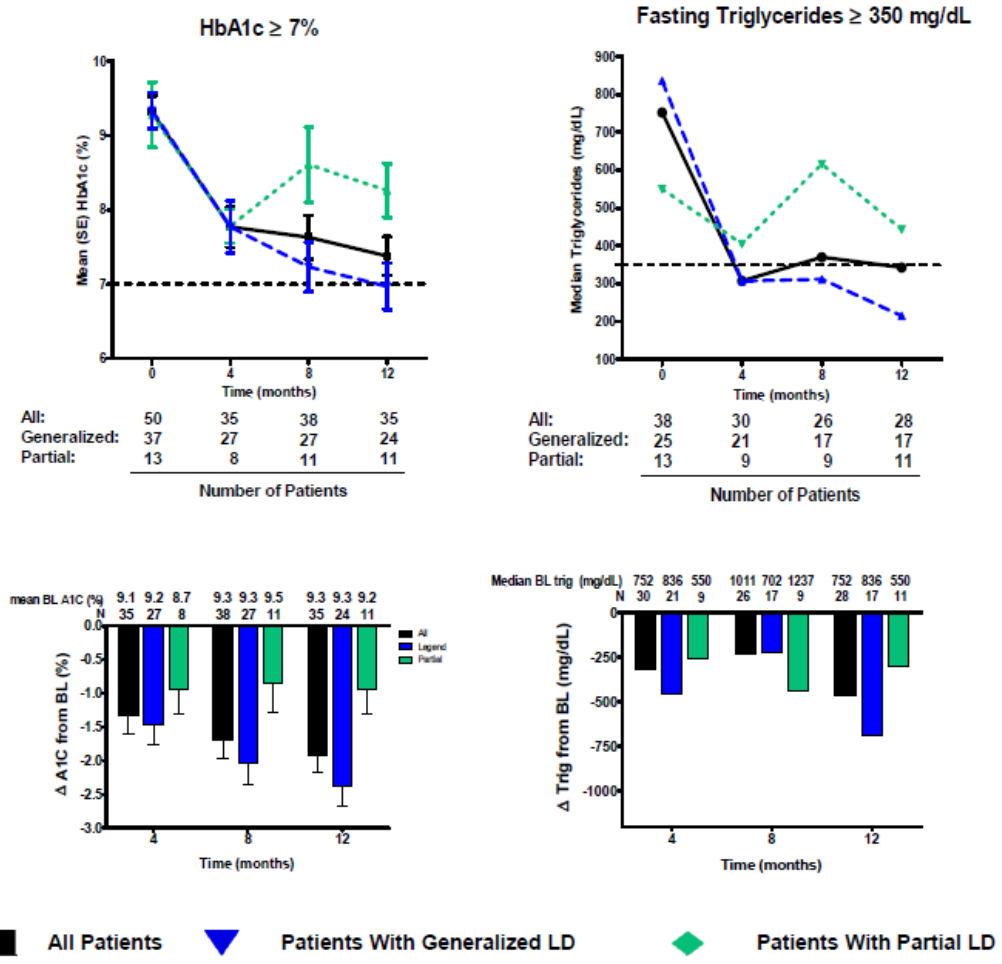


[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time 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.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 2

Figure 21. Key Efficacy Parameters in Patients with Baseline HbA1c 7% or Greater, or TG 350 mg/dL or Greater: All Patients, Generalized Lipodystrophy, and Partial Lipodystrophy (NIH; Observed Data for Each Efficacy Parameter [1])



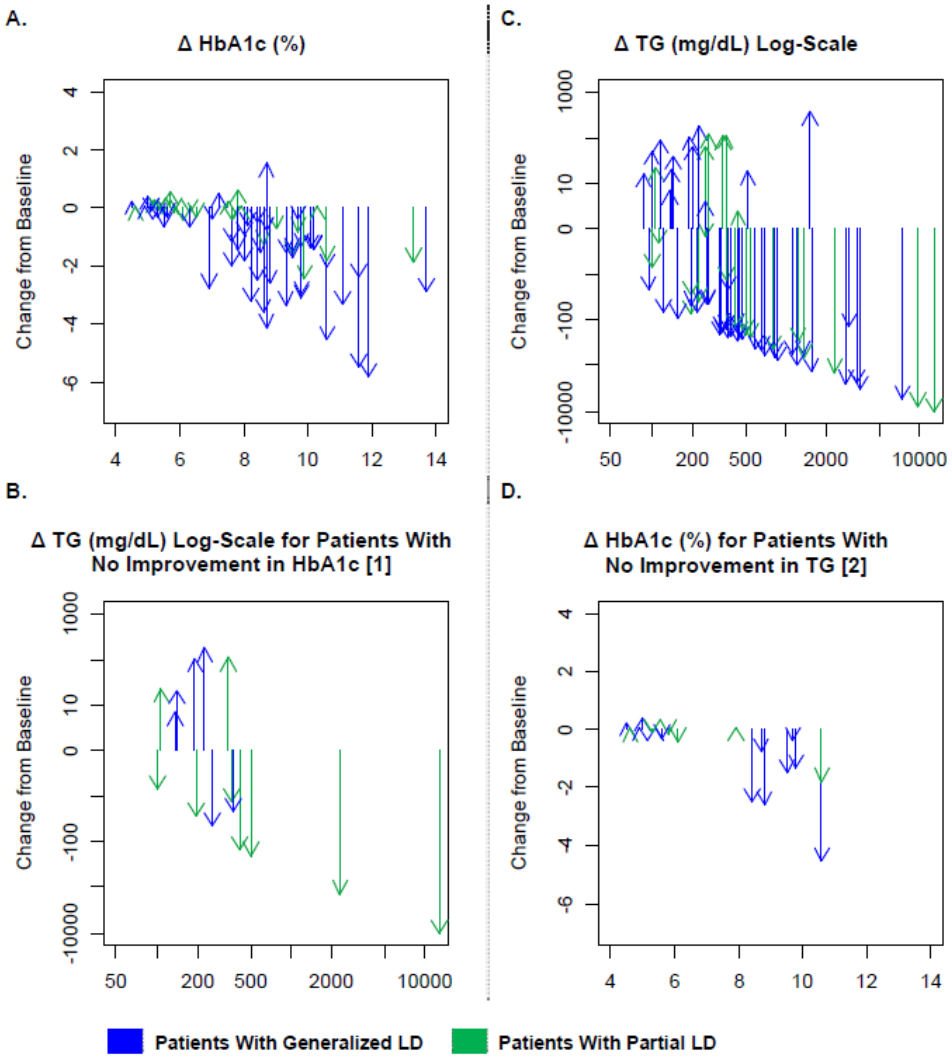
[1] The N at each time point represents all ITT patients with data for that parameter at the specified time point. For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and the specified time point. Note that the N at a given time 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.

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 3

Reviewer comment: These figures further support metreleptin benefit for patients with generalized lipodystrophy who have significant metabolic complications (notwithstanding the reviewer's comment about baseline abnormalities, above). Even in the subgroup with elevated HbA1c and TG at baseline, patients with partial lipodystrophy appear to have attenuated responses as compared with generalized patients.

Figure 22 demonstrates the relationship between the severity of baseline metabolic abnormalities (HbA1c and TG) and changes in these parameters over time.

Figure 22. Average Change from Baseline in HbA1c and Fasting TG during the First 12 Months of Metreleptin Treatment versus Baseline Value for Individual Patients: Generalized and Partial Lipodystrophy, NIH Trials



[1] No improvement is defined as patients with ≥0% increase in HbA1c.
[2] No improvement is defined as patients with ≥0 mg/dL increase in TG.

Note: The x-axis represents the baseline value
Source: Clinical Efficacy Update, Figure 4

Reviewer note: In Chart B, the patient with the largest downward arrow is presumed to be Patient 90152 (30 yo F FPL), whose Baseline TG was 12697 mg/dL and Month 8 TG was 2320 mg/dL. At Month 18, the patient's TG was 7557 mg/dL, reflecting the variability of TG over time.

Reviewer comments: Note that while most patients have a favorable (or unchanged) HbA1c response, the TG response is more variable. This may be that TG is influenced by factors other than insulin resistance (e.g., short-term changes in dietary composition, genetic factors, etc.). This suggests that while TG improvements in patients with lipodystrophy treated with metreleptin may be due to improvements in insulin resistance, to the extent that patients also have hypertriglyceridemia for other reasons (potentially related to the type of lipodystrophy), metreleptin's effects may be more variable. As noted previously, without a placebo control it is challenging to interpret some of these findings and accurately estimate the treatment effect.

A review of patients who only have uncontrolled severe hypertriglyceridemia (TG 500 mg/dL or greater) without uncontrolled diabetes (HbA1c 7 mg/dL or greater), suggested that (1) this is an uncommon finding (4%), and (2) in the case of two of the three patients with partial lipodystrophy, improvements in TG were confounded by concomitant medication changes. The one-year-old patient with CGL (90168) who had improvements in TG only, not HbA1c, clearly had severe insulin resistance at baseline, with a fasting insulin concentration of 303 µU/mL (not shown in the table below).

Table 38. Triglyceride Values Over Time and Relevant Concomitant Medications for Patients Enrolling with only Severe Hypertriglyceridemia Without Associated Uncontrolled Diabetes Mellitus

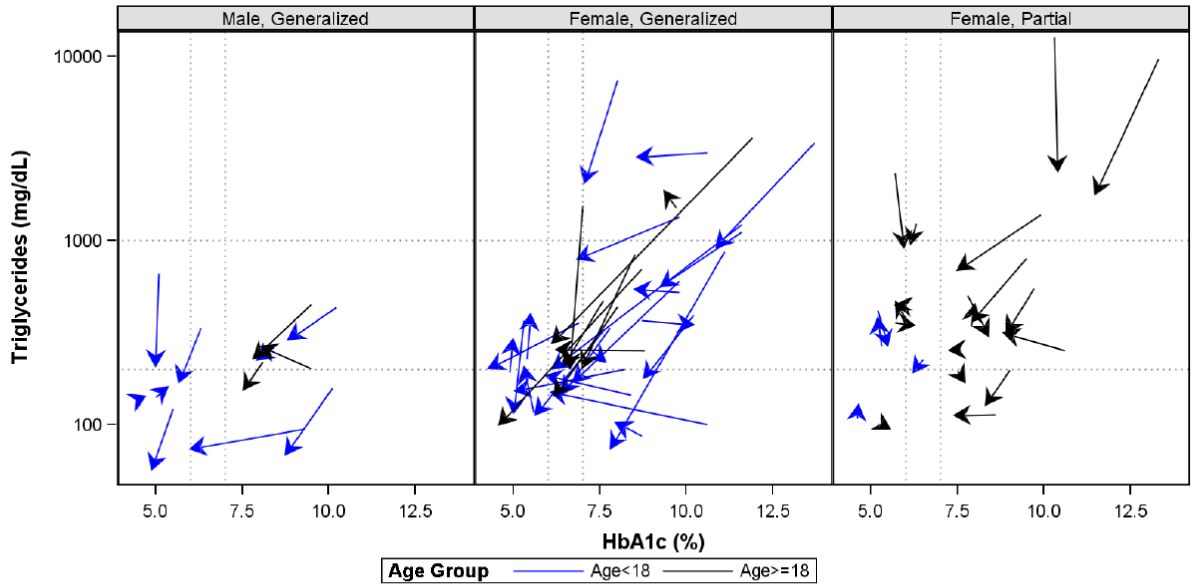
Patient ID / Demog / BL HbA1c	NIH: Study day (Visit) FHA101: Visit (description)	TG (mg/dL)	Medication comments
NIH Patient 90121 / 32 yo F FPL / 5.7%	-4 (Baseline)	2324	Atorvastatin at baseline
	122		Started fish oil, fenofibrate
	132 (Month 4)	530	
	286 (Month 8)	752	
	412 (Month 12)	1825	
	571 (Month 18)	7010	
NIH Patient 90132 / 18 yo F APL / 6.3%	-7 (Baseline)	1237	
	112 (Month 4)	1048	
	240 (Month 8)	1578	
	357		Started fenofibrate
	365 (Month 12)	494	
NIH Patient 90168 / 1 yo M CGL / 5.1%	-1 (Baseline)	663	
	87 (Month 4)	204	
FHA101 Patient 648018 / 40 yo F APL / 5.7%	Visit 1 (Day 1)	1243	Fish oil at baseline
	Visit 5 (Month 3)	436	
	Visit 6 (Month 6)	399	
	Visit 7 (Month 9)	471	

Source: Reviewer generated from BLA 125390 datasets: DLABS, DLABS 2, DCLINLAB

The following figures are provided as additional summaries of the relationship between HbA1c and TG changes in the NIH trials.

In Figure 23, each patient is represented by a vector, whose start represents the baseline HbA1c (horizontal axis) and TG (vertical axis) value, and whose pointed end represents the average of that patient's post-baseline values through Month 12 for HbA1c (arithmetic mean) and TG (geometric mean). Thus, vectors that point from right to left indicate a reduction in HbA1c at Month 12, vectors that point downward reflect improvement in TG concentrations, and vectors pointing diagonally downward and to the left represent improvement in both HbA1c and TG. Vectors are presented for patients who had HbA1c and TG data available for baseline as well as at least one post-baseline value. Furthermore, this plot includes color coding to indicate pediatric (less than 18 years) versus adult (18 years or older) patients.

Figure 23. Change From Baseline to Average Post-Baseline Values of HbA1c and Geometric Mean of Post-Baseline Values of TG Up to 12 Months for Individual Patients by Sex and Generalized versus Partial Lipodystrophy (NIH Trials)

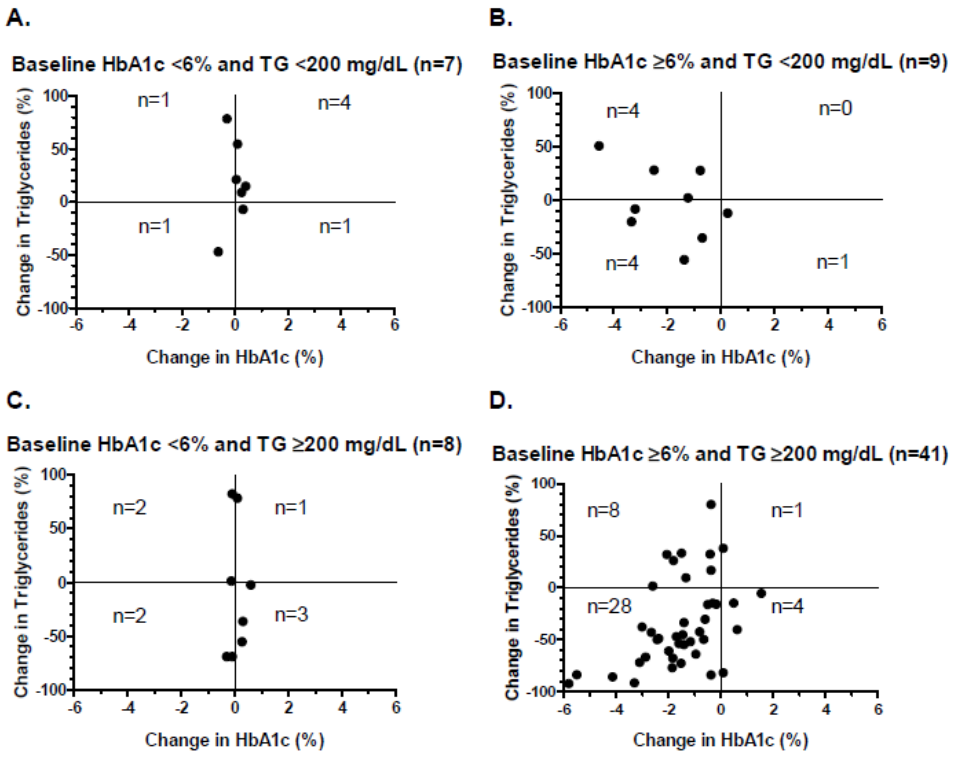


[1] Horizontal Axes: HbA1c values. Vertical Axes: Triglyceride values. Arrows begin at the BL value (A1c or TG) and end with post baseline value (pointed end of arrow.)
Length of Arrow: Magnitude of change from baseline with upward arrow (increase from baseline) and downward arrow (decrease from baseline).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

Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 10

Figure 24 provides an alternative view of the above figure, with the percent change in TG plotted against the change in HbA1c (average of the first 12 months of treatment) for each patient with at least one post-baseline value during the initial 12 months of metreleptin treatment, according to the baseline metabolic status.

Figure 24. Change From Baseline to Average Post-Baseline Values of HbA1c and Percent Reduction in TG Up to 12 Months for Individual Patients by Baseline Metabolic Abnormality Category (NIH; Patients with Baseline and at Least One Post-Baseline Measurement)



Source: BLA 125390, submission 27 Mar 2013; Clinical Efficacy Update, Figure 6

An exploration was done of factors that might predict which individual patients within subpopulations respond beneficially to metreleptin. As demonstrated above, patients with generalized lipodystrophy, particularly those with uncontrolled metabolic disease appear to have the most robust response. Baseline fasting leptin could also be an important factor; particularly given the observation that patients in earlier versions of the NIH protocol utilized lower fasting leptin values as a key eligibility criterion. Over the entire cohort, patients with generalized lipodystrophy had mean fasting leptin (SD) of 1.3 ng/mL (1.1) and those with partial lipodystrophy had a value of 4.9 ng/mL (3.1).

The relationship between baseline leptin and response to metreleptin treatment was specifically evaluated in patients with partial lipodystrophy who had a wider range of baseline leptin values compared with patients with generalized lipodystrophy who were almost all “low” leptin (i.e., less than 2 ng/mL, males; less than 4 ng/mL, females). All three endpoints (HBA1c, FPG, and TG) demonstrated greater change from baseline for patients with lower baseline leptin concentration in patients with partial lipodystrophy.

Table 39. Change From Baseline to Month 12 in Key Efficacy Parameters by Leptin Level Categories, NIH Trials

	Mean (SE) HbA1c (%)			Mean (SE) FPG (mg/dL)			Median TG (mg/dL)			
Leptin Level Category (ng/mL)	N	BL [3]	Δ from BL at Mo. 12	N	BL [3]	Δ from BL at Mo 12	N	BL [3]	Δ from BL at Mo. 12	% Δ from BL at Mo.12
GENERALIZED										
All										
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	26	8.6 (0.4)	-2.1 (0.3)	28	175.5 (17.3)	-47.6 (18.4)	28	415	-247	-64
Min, Max		4.9, 13.7	-5.8, 0.7		71, 478	-232, 271		87, 7420	-5977, 473	-93, 90
≥4 (Female) / ≥2 (Male)										
Mean (SE) /Median [1]	1	10.1 (na)	-1.6 (na)	1	200.0 (na)	-134.0 (na)	1	158.0	-105.0	-66.5
Min, Max		na	na		na	na		na	na	na
Elevated Baseline	**Baseline HbA1c ≥ 6%**			**Baseline FPG ≥ 126 mg/dL**			**Baseline TG ≥ 200 mg/dL**			
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	23	9.1 (0.4)	-2.4 (0.3)	18	219.1 (20.4)	-86.7 (18.2)	20	562	-395	-74
Min, Max		6.3, 13.7	-5.8, 0.7		126, 478	-232, 74		261, 7420	-5977, 473	-93, 90
≥4 (Female) / ≥2 (Male)										
Mean (SE) /Median [1]	1	10.1 (na)	-1.6 (na)	1	200.0 (na)	-134.0 (na)	-	-	-	-
Min, Max		na	na		na	na		-	-	-
PARTIAL [2]										
All										
<4 (Female)										
Mean (SE) /Median [1]	10	7.6 (0.9)	-0.9 (0.4)	10	177.8 (32.5)	-55.5 (26.7)	10	609	-237	-29
Min, Max		4.6, 13.3	-3.1, 0.6		65, 367	-224, 17		108, 9702	-8866, 521	-91, 194
≥4 (Female)										
Mean (SE) /Median [1]	11	7.5 (0.5)	-0.1 (0.2)	11	135.7 (21.8)	-10.7 (12.5)	11	343	-64	-18
Min, Max		5.3, 10.6	-0.7, 0.9		49, 284	-88, 48		101, 550	-298, 115	-54, 40
Elevated Baseline	**Baseline HbA1c ≥ 6%**			**Baseline FPG ≥ 126 mg/dL**			**Baseline TG ≥ 200 mg/dL**			
<4 (Female)										
Mean (SE) /Median [1]	6	9.2 (1.0)	-1.6 (0.4)	6	239.0 (35.6)	-99.2 (34.4)	8	1020	-429	-37
Min, Max		6.3, 13.3	-3.1, -0.3		151, 367	-224, -28		255, 9702	-8866, 521	-91, 194
≥4 (Female)										
Mean (SE) /Median [1]	8	8.1 (0.5)	-0.2 (0.2)	5	199.2 (25.7)	-31.8 (23.9)	8	358.0	-65	-16
Min, Max		6.1, 10.6	-0.7, 0.9		145, 284	-88, 48		227, 550	-298, 115	-54, 40

[1] Data represent Mean (SE) for HbA1c and FPG; Median for TG;
[2] All patients with partial LD in NIH were females.

[3] For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and Month 12.

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 5

Table 40. Change From Baseline to Month 12 in Key Efficacy Parameters by Leptin Level Categories, FHA101 Partial Lipodystrophy Patients[††††††]

	HbA1c (%)			FPG (mg/dL)			TG (mg/dL)			
Leptin Level Category (ng/mL)	N	BL [2]	% Δ from BL at Mo. 12	N	BL [2]	% Δ from BL at Mo. 12	N	BL [2]	Δ from BL at Month 12	% Δ from BL at Mo. 12
PARTIAL										
All										
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	1	11.1 (na)	-4.7 (na)	1	242.0 (na)	-127.0 (na)	1	193	-101	-52
Min, Max		na	na		na	na		na	na	
≥4 (Female) / ≥2 (Male)										
Mean (SE) / Median [1]	7	8.3 (0.6)	-0.3 (0.3)	7	163.0 (16.7)	-29.9 (21.7)	7	341	-61	-18
Min, Max		6.5, 11.0	-2.0, 0.4		92, 211	-114, 43		66, 919	-644, 129	-70, 39
Elevated Baseline	**Baseline HbA1c ≥6%**			**Baseline FPG ≥126 mg/dL**			**Baseline TG ≥ 200 mg/dL**			
<4 (Female) / <2 (Male)										
Mean (SE) /Median [1]	1	11.1 (na)	-4.7 (na)	1	242.0 (na)	-127.0 (na)	-	-	-	-
Min, Max		na	na		na	na	-	-	-	-
≥4 (Female) / ≥2 (Male)										
Mean (SE) / Median [1]	7	8.3 (0.6)	-0.3 (0.3)	6	174.8 (14.0)	-36.8 (24.3)	5	341	-166	-47
Min, Max		6.5, 11.0	-2.0, 0.4		130, 211	-114, 43		304, 919	-644, 129	-70, 38

[1] Data represent Mean (SE) for HbA1c and FPG; Median for TG.
[2] For analysis of change from baseline, the N reflects the number of patients with data for that specific parameter at baseline and Month 12.

Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 7

By Age

The pediatric population (N = 39) in the NIH trials changed over time, as the age criterion was lowered as the protocol progressed. The pediatric population was predominantly female (77%) and white (54%). Of the 39 pediatric patients, 35 (90%) were diagnosed with generalized lipodystrophy (26 congenital and nine acquired), and four patients (10%) were diagnosed with partial lipodystrophy (two familial and two acquired). The mean age of the pediatric population at baseline was 12 years (range: one to 17 years), with 17 (44%) 12 years old or younger and 22 (56%) older than 12 to younger than 18 years old.

While baseline HbA1c abnormalities were comparable in pediatric and adult patients (8.1% pediatric, 8.4% adult), there was a greater percentage of pediatric patients with HbA1c less than 6% (n = 11, 28%) versus adults (n = 4, 12%).

Baseline TG levels were higher in adult versus pediatric patients (mean TG 1346 mg/dL versus 791 mg/dL), although this was driven by two adult patients having TG values greater than 9000 mg/dL. The median TG in adult patients was 446.5 mg/dL versus 335.0 mg/dL in pediatric patients

The percentage of pediatric patients with TG less than 200 mg/dL was higher compared to adults (n = 13, 33% and n = 4, 12%, respectively). (Of note, 95 percent of children and adolescents 12 to 19 years old in the general United States population have a TG

[††††††] Results in the 5 patients in FHA101 with generalized lipodystrophy are presented separately in Table 29; all patients (with leptin concentrations available) were in the "low" leptin category.

concentration between 61-88 mg/dL; in children and adolescents with obesity 6 to 19 years old, the TG range is from 79-94 mg/dL.[27])

Of seven patients with baseline HbA1c less than 6% and TG less than 200 mg/dL (enrolled on the basis of insulin resistance), six (15%) were pediatric compared to one (3%) adult. However, these pediatric patients were more likely to have liver findings reported at baseline. A greater percentage of pediatric patients (67- 80%) had elevated liver enzymes compared to adult patients (42- 46%), and mean AST and ALT were higher in pediatric compared to adult patients. Per the NIH investigator, patients enrolled in the study based on insulin resistance were generally enrolled only if they also had evidence of clinically significant liver disease related to lipodystrophy (hepatic steatosis / steatohepatitis).

See Table 34 and Figure 23 for a summary of results by age groups.

Reviewer comment: The subgroup results presented in Table 34 suggest that children less than 12 years of age may receive less benefit from metreleptin than other age groups. However, there were some young children who did appear to respond to treatment. The likely reason that the young children subgroup (i.e., less than 12 years of age) did not demonstrate robust mean changes was that this group was less likely to have significant abnormalities in baseline HbA1c and TG.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

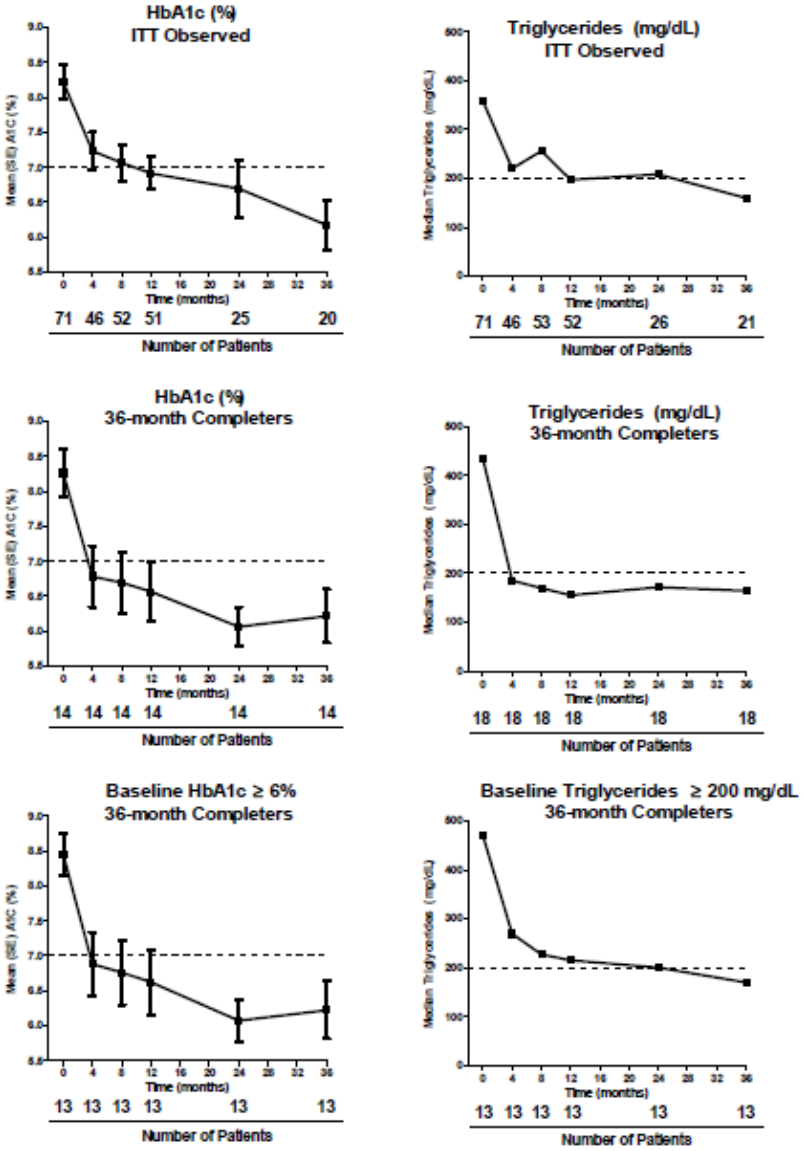
The proposed dosing recommendations in the label were based on the dosing regimen that the NIH investigators used and became comfortable with over time[‡‡‡‡‡‡] and were ultimately adopted by the treatment protocol (FHA101).

[‡‡‡‡‡‡] The following comment in the NIH protocol regarding dose adjustments was noted (emphasis added):
In individuals above the age of 5 years, the dose of metreleptin will be increased beyond 0.12 mg/kg/day only if there is a clear decline in metabolic status without alternative explanations for the metabolic change (such as an infection, noncompliance, or dietary indiscretion). ***It is important to note this because of the wide range of variation in the clinical presentation of these patients it is impossible to define pre-determined thresholds of metabolic parameters that would appropriately guide dose modifications. Instead, the PI will use best clinical judgment to make dose modifications based on the constellation of metabolic and clinical data available to each patient.*** *The dose of metreleptin can be increased from 0.08 mg/kg/day after the 4-month follow-up. All dose escalations will be performed in increments of 0.02 mg/kg/day for females 10 years of age and older, and 0.015 mg/kg/day in all other study participants. Only one dose increase may be done per week, in order to evaluate the effect on body weight and on injection sites. Dose escalation will be capped such that the total dose administered will not exceed 0.24 mg/kg/day for any patient without seeking prior permission from the FDA, the IRB, and Amylin, Inc., the manufacturer of metreleptin. If subjects do not tolerate a higher dose level, they can continue the study at the next lowest tolerated dose.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Although some patients were exposed to metreleptin for years, it is notable that many patients prematurely discontinued from the trial and/or were non-compliant. Therefore, efficacy in patients treated for the long-term could be confounded by relevant patient characteristics (e.g., willing to return for visits, highly motivated, highly compliant, etc.). Nevertheless, longer-term data are available. The evaluation of greater duration of treatment has to be balanced against the diminishing numbers of patients with data at later time points; therefore, the sponsor chose a 36-month time point as a reasonable balance of these factors to assess durability of effect. The following figures present HbA1c and TG over 36 months in all patients available (ITT), “completers” (i.e., patients who were available at all time points), and patients with elevated baseline HbA1c and TG values.

Figure 25. Mean (SE) HbA1c and Median TG from Baseline to Month 36 (NIH; Observed, 36 Month Completers, and 36 Month Completers with Baseline HbA1c 6% or Greater and TG 200 mg/dL or Greater)



[1] Dashed lines denote common treatment goals and/or diagnostic criteria for HbA1c of 7%; TG of 200 mg/dL.
[2] 36-month completers are defined as receiving at least 36 months of metreleptin treatment and having data for the specified efficacy measure at baseline, M4, M8, M12, M24, and M36.

Source: Clinical Efficacy Update, Figure 11

Reviewer comment: Note that 36-month completers for HbA1c and TG only make up 19% and 25%, respectively, of the total population. Therefore, it is unknown how representative these results are of the lipodystrophy population overall.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Patients with lipodystrophy can present with significant co-morbidities, often as a result of the complications of lipodystrophy (e.g., pancreatitis, atherosclerosis, cirrhosis), or reflecting an underlying autoimmune disease as in the case of many patients with acquired lipodystrophies. It is particularly challenging to assess the safety of metreleptin and adjudicate its role in a variety of adverse events, given the high background incidence of co-morbid disease and the theoretical possibility that metreleptin may exacerbate certain conditions via its activation of the Janus kinase signal transducer and activator of transcription (JAK-STAT) and other intracellular pathways, as well as its effects on the immune system. Safety issues of particular interest in this development program include the following:

- T-cell lymphoma: Three cases of T-cell lymphoma have been reported in patients with AGL in the NIH trials. Two of the cases occurred in patients with hematological disease (neutropenia, lymphadenopathy) at baseline and were on confounding medications, such as G-CSF and erythropoietin. A third patient (13-year-old with AGL) did not have any known hematological disorders or other confounding factors prior to developing lymphoma, aside from the AGL diagnosis. Leptin is a cytokine that exerts its effect by binding to the leptin receptor on cell surfaces and activating the JAK-STAT intracellular pathway. Leptin signaling via JAK-STAT and other pathways promotes cell growth and survival and inhibits apoptosis. Dysregulation of STAT proteins and signalling contributes to the pathogenesis of some malignancies. It is unknown if metreleptin could promote the progression of lymphoma or other malignancies in a patient population that is predisposed to these diseases. Of note, hematological malignancies, including T-cell lymphoma, have been reported in the literature in patients with lipodystrophy not treated with metreleptin.

- Immunogenicity: Metreleptin is highly immunogenic. The majority of patients exposed in clinical trials developed anti-leptin antibodies. Development of binding antibodies is associated with supraphysiological concentrations of circulating leptin, as well as inflammatory injection site adverse events. To some extent, the long-term clinical sequelae of antibody development are unknown. Nevertheless, a number of adverse events associated with the development of antibodies with neutralizing activity, particularly in patients treated with metreleptin in the development program for obesity (not currently active), has highlighted a potential risk for off-label use. Three patients in the obesity program have been identified with the development of neutralizing antibodies. All three patients presented with high antibody titer, low

leptin concentrations, and excessive body weight gain (13 kg to 66 kg above baseline body weight). One patient in the lipodystrophy program was recently identified as having developed high-potency, highly reproducible, neutralizing anti-leptin antibodies. This patient, a 19-year-old female with CGL, appears to have had some loss of efficacy (HbA1c) based on the last measured efficacy parameters and, perhaps more significantly, has had five hospitalizations as a result of various bacterial infections over this past summer. Because of the role that leptin plays in the functioning of the immune system, it is theoretically possible that neutralizing antibodies to leptin could have implications for immune functioning (i.e., immunodeficiency), even in patients with very low endogenous leptin. An additional unanswered question related to the development of neutralizing antibodies in the lipodystrophy population is whether a risk of maternal-fetal transfer of neutralizing antibodies exists, and whether a baby born to a mother with neutralizing antibodies could develop a congenital leptin deficiency-like condition.

- Autoimmunity: Leptin activates a number of cell signaling pathways important in T-cell activity and is permissive in cellular proliferation and cytokine production. Therefore, exacerbation of autoimmunity is a theoretical concern, given leptin's role in the immune system. In the NIH trials, adverse events of autoimmune hepatitis and membranoproliferative glomerulonephritis (associated with massive proteinuria and renal failure) exacerbations were seen in some patients with AGL treated with metreleptin. The contribution of metreleptin in these cases is unknown, but appears plausible.

- Other Immune-Related Adverse Events: Other potentially immune-related adverse events in the lipodystrophy trials included urticaria, pruritus, arthralgia, asthma, rash, and facial swelling. (A single anaphylactic reaction was thought likely food-related.) In a summary of five pooled placebo-controlled obesity trials, severe injection site reactions were reported in 0.9% of metreleptin-treated patients versus 0.3% of placebo-treated patients. Other injection-site adverse events occurring more frequently in metreleptin-treated compared to placebo-treated patients included injection site erythema (10.8% versus 0.6%), injection site inflammation (4.8% versus 0.6%), injection site edema (2.3% versus 0.0%), injection site pruritus (8.0% versus 1.7%), and injection site rash (2.4% versus 0.0%). In the pooled obesity trials, non-injection site reaction adverse events reported as associated with hypersensitivity were experienced by 14% of metreleptin-treated patients versus 8% of placebo-treated patients. A serious adverse event of systemic hypersensitivity occurred in an obesity trial participant.

- Hypoglycemia: Hypoglycemia was the most frequent adverse event reported in the lipodystrophy trials. In the NIH trials, hypoglycemia was reported only in those patients receiving concomitant insulin therapy with or without oral anti-hyperglycemic agents. No severe hypoglycemia events (e.g., requiring the assistance of another individual) were reported. In FHA101, one patient experienced a severe event of

hypoglycemia that required assistance from another person. In this trial, most events of hypoglycemia occurred in patients who were receiving concomitant insulin therapy or a sulfonylurea with or without other oral antihyperglycemic agents, except one patient who experienced an event of hypoglycemia while on metformin only. In patients with type 2 diabetes mellitus in the pooled obesity trials, 14.3% of patients on metreleptin and 5.0% of patients on placebo reported hypoglycemia.

- Pancreatitis: Patients with lipodystrophy are predisposed to acute pancreatitis, due to marked hypertriglyceridemia (often defined as TG greater than 1000 mg/dL). In the NIH trials, 16 (22.2%) patients had a medical history of pancreatitis and 4 (5.6%) patients had a history of recurrent pancreatitis. Although some patients treated with metreleptin appeared to have significant improvement in TG concentrations, many patients continued to have high or fluctuating TGs, and adverse events of pancreatitis were seen in the lipodystrophy trials. As there was no control group, and the trials were not powered to detect either an improvement or worsening in pancreatitis, the potential contribution of metreleptin on pancreatitis events in a patient population predisposed to this adverse event is unknown. The sponsor has proposed that patients who developed pancreatitis in the lipodystrophy program were non-compliant or they discontinued or interrupted metreleptin too rapidly with subsequent rebound in serum TG. Of note, in the pooled obesity trials, one patient treated with metreleptin (out of 784) had a serious adverse event of pancreatitis, versus no placebo-treated patients (out of 351).

- Liver-Related Adverse Events: Patients with lipodystrophy who have undergone liver biopsy have been described to fall within the spectrum of non-alcoholic fatty liver disease (NAFLD), from none to inflammation and fibrosis (including cirrhosis), as well as having other liver diseases such as autoimmune hepatitis. Seven patients in the lipodystrophy development program had adverse events related to the liver; all had liver-related abnormalities at baseline. Notably, five out of the seven events occurred in patients with AGL, three of whom had known autoimmune hepatitis at baseline. No patient in the lipodystrophy program met the laboratory criteria for Hy's law (i.e., ALT or AST greater than 3x ULN accompanied by total bilirubin greater than 2x ULN); however, a patient in the NIH trial (18-year-old female with AGL) with a history of cirrhosis died due to progressive end-stage liver disease.

- Nephropathy: Proteinuric nephropathies have been associated with lipodystrophy, and approximately one third of the patients in the lipodystrophy program had a medical history of proteinuria. In the NIH trials, worsening of renal disease (proteinuria or creatinine increases or adverse events relevant to proteinuric nephropathies) was seen in 12 patients, and five of those patients were known to have ultimately progressed to end-stage renal disease, despite transient improvements in proteinuria in some cases. The contribution of metreleptin to the worsening of underlying renal disease is unknown; however, an effect on autoimmune-related renal disease in patients with AGL appears plausible.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following table is similar to the table presented in Section 5.1 (Table 6), with the exception of descriptions of additional investigational trials that have been conducted with metreleptin in a variety of patient populations. Where available, the safety data from these trials are presented in this section.

Table 41. Studies Supporting the Metreleptin for Lipodystrophy BLA and Other Studies and Compassionate Use Treatment Involving Metreleptin Administration

Study	Patient Population	Number of Metreleptin-Treated Patients	Position in BLA	Endpoints Supported
NIH Trials 991265/20010769 [1]	Lipodystrophy patients	72 [2]	Pivotal	Safety and efficacy
Treatment IND FHA101 [1]	Lipodystrophy patients	28 [3]	Supporting	Safety and efficacy
Amgen 5-trial ISS (metreleptin monotherapy)	Obese patients without lipodystrophy	784	Supporting	Safety (including immunogenicity)
10 other Amgen obesity trials (metreleptin monotherapy)	Obese patients without lipodystrophy	379 [4]	Supporting	Immunogenicity
Amylin obesity program (metreleptin/pramlintide combination)	Obese patients without lipodystrophy	615	Supporting	Immunogenicity
Other investigator-initiated trials [1]	Lipodystrophy patients Rabson-Mendenhall	92 [5]	[7]	[7]
Compassionate use treatment [1]	Lipodystrophy patients	51 [5][6]	[7]	[7]
Compassionate use treatment [1]	Congenital leptin deficient patients	18 [5]	[7]	[7]
Other investigator-initiated trials in other indications	HIV-associated lipodystrophy, obesity, NASH, HA, type 1 DM, healthy subjects	248	[7]	[7]

NASH=non-alcoholic steatohepatitis; HA=hypothalamic amenorrhea; DM=diabetes mellitus
[1] ongoing trials or ongoing treatment, except investigator-initiated study with C. Levy Marchal as principal investigator
[2] As of 11 July 2011 data cut
[3] As of 7 Mar 2012 data cut
[4] Excludes 4 patients with congenital leptin deficiency treated with metreleptin in Amgen trial 970161
[5] As of January 2013
[6] Excludes patients who initiated metreleptin treatment though other trials (e.g., NIH trials, other investigator-initiated trials)
[7] Note that although these trials were not included in the BLA, in response to an FDA information request the sponsor provided some limited safety information; see Section 7.7, Additional Submissions / Safety Issues; individual adverse events were also presented in some other sections of the safety review

Source: BLA 125390, Section 2.5 Clinical Overview, date 27 Mar 2013; sponsor response to FDA 24 Jun 2013, Table 3

A total of 13 clinical studies were conducted by Amgen under IND 50,259 to support the development of metreleptin for the treatment of obesity. Amgen, who was at the time of the initial proposal for the BLA, the sponsor of these data, selected five of these trials to form the basis of the supporting ("supplemental") integrated summary of safety (ISS). Criteria for inclusion into this supplemental ISS include: Phase 2, randomized, placebo-controlled trials of metreleptin administered by subcutaneous injection to overweight/obese individuals (with or without type 2 diabetes) with treatment duration of at least 12 weeks. The obesity development program was terminated prior to initiation of any Phase 3 studies.

The five studies that met these criteria were:

- LEPT-970164, LEPT-970213, and LEPT-980236, which were conducted in overweight/obese patients without type 2 diabetes; and

- LEPT-970171 and LEPT-970188 conducted in overweight/obese patients with type 2 diabetes.

Among these, LEPT-980236 was designed as a 52-week trial, with a planned sample size of 340 patients randomized to treatment. Although this trial was terminated early due to the sponsor's discontinuation of the metreleptin for obesity development program, and none of the randomized patients completed the study, it was included in the ISS because most (67%) of the 267 patients randomized to treatment completed 12 weeks of treatment and 44% completed 24 weeks of treatment.

Reviewer comment: FDA and the sponsor agreed that data from these five obesity trials could be pooled to support the safety assessment (see Table 4). There are limitations to the pooling approach, including the variable trial durations, the premature discontinuation of the 52-week trial, and a trial design (a different trial) that included an induction period in which all patients were treated with metreleptin prior to randomization (decribed in Section 7.3.2, Nonfatal Serious Adverse Events). The advantages to the pooling are that there are a relatively large number of patients, and there is a placebo control.

Additional trials evaluated for certain safety issues (i.e., deaths, nonfatal serious adverse events, and adverse events of special interest) include Amgen trials evaluating metreleptin for obesity that were not included in the ISS, and trials from the Amylin metreleptin-pramlintide combination development program for obesity. These trials are listed below.

Table 42. Summary of Studies from the Amylin Metreleptin + Pramlintide Program (DFA) and the Amgen Metreleptin Trials not Included in the Five-Trial ISS

Study	Design	Patient Population	Number Treated With Metreleptin
DFA102/102E	Phase 2, randomized, double-blind, placebo-controlled, 28-week dose-ranging study with an open-label extension up to 52 weeks	Obese without LD	496 [1]
DFA103	Phase 1, open-label, cross-over bioavailability study	Obese and overweight without LD	78
DFA104	Phase 2B, randomized, double-blind, placebo-controlled, study to examine the efficacy and safety following a low-calorie diet lead-in	Obese without LD	36
Amgen Studies			
LEPT-950272	Randomized, double-blind, placebo-controlled, 24-week dose-ascending study	Non obese and obese without LD	177
LEPT-960176	Follow-up open-label, 24-month study	Obese without LD	151
LEPT-960240	Randomized, double-blind, placebo-controlled, CSCI, individual ascending-dose, 30-week study	Obese without LD	23
LEPT-970161	Open-label dose-ascending study	Obese with congenital leptin deficiency (due to leptin gene mutation)	4
LEPT-970121	Randomized, double-blind, placebo-controlled, IV, dose- ascending, 30-day study	Healthy	83
LEPT-970211	Randomized, double-blind, placebo-controlled, 16-week dose-ascending study	Obese without LD	5
LEPT-980219	Randomized, double-blind, placebo-controlled, 24-week study	Non-obese and obese without LD, with type 2 diabetes treated with Met or Met in combination with a SU	44
LEPT-980145	Randomized, double-blind, placebo-controlled, 24-week dose-ascending study	Overweight and obese without LD, with type 2 diabetes	6 (A-100)
LEPT-980225	Randomized, double-blind, placebo-controlled, 24-week study	Overweight without LD, with type 2 diabetes treated with insulin alone or insulin in	18
LEPT-980298	Phase 1, PK comparison and safety study	Obese without LD	24 (A100/300)[2]
		Total Treated with Metreleptin	1228

Met=metreleptin; pram=pramlintide; LD=lipodystrophy; SU=sulfonylurea, Met=metformin, CSCI=continuous subcutaneous infusion, IV=intravenous, PK=pharmacokinetic
[1] DFA102E is an extension study of DFA102 with 273 subjects enrolled in the extension.

[2] A-100 is Amgen's designation for metreleptin and A-300 is an analog of A-100 with a sequence modification to improve solubility under physiological condition.

Source: Response to FDA Request for Information Dated 24-May-2013; Question 1, Table 1-1

7.1.2 Categorization of Adverse Events

Although the sponsor utilized MedDRA[28] to categorize adverse events, because of the relatively small size of the database, many adverse events are presented in list form and are counted according to clinical scenarios (e.g., pancreatitis, potentially immune-related, etc).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The lipodystrophy trials are presented for safety as they were for efficacy: adverse events, laboratory data, and vital signs are tabulated for the NIH trials and FHA101 trial.

In the ISS (five Amgen obesity trials), all patients who received at least one injection of randomized study medication (metreleptin or placebo) were included in the analyses. An exception is for LEPT-970213 in which eligible participants were randomized into the treatment period (Part C) after a three-week dietary lead-in period (Part A) and a four-week metreleptin 10 mg BID induction period (Part B). All 228 participants who received at least one dose of metreleptin during the metreleptin induction period (Part B) were included and counted as metreleptin-treated. Among these 228 patients, 189 patients (126 to metreleptin and 63 to placebo) were randomized into the 24-week treatment period (Part C). The 63 patients who were randomized to placebo treatment in the 24-week treatment period (Part C) were counted as both metreleptin-treated (induction period) and placebo-treated (randomized treatment period), and the analyses were conducted as appropriate depending on the period when data were collected.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 43. Number of Patients in Completed and Ongoing Studies Who Received at Least One Dose of Metreleptin as of the Original BLA Cutoffs and the Clinical Safety Update Cutoffs

Trial	Original BLA	Clinical Safety Update
NIH		
N	55	72
Data Cutoff Date	31 July 2009	11 July 2011
FHA101		
N	10	28
Data Cutoff Date	14 June 2010	07 March 2012
Total	65	100

Source: BLA 125390 Clinical Safety Update, 27 March 2013 Submission, Table 1

The data cutoffs for the FHA101 trial were more recent compared to the NIH trial due to the reported logistical issues associated with performing a data cut for an investigator-sponsored clinical study versus the Amylin-sponsored FHA101. In addition, patients in FHA101 generally returned every three months for follow-up visits whereas study visits were more infrequent in the NIH study due to travel considerations for the majority of the patients.

Integrated safety results from five Phase 2, randomized, placebo-controlled trials of metreleptin administered by subcutaneous injection in 1072 overweight and obese patients (784 exposed to metreleptin) with or without type 2 diabetes with treatment duration of at least 12 weeks, with a range of exposure from one day up to 42 weeks, provide supplemental safety data for metreleptin use in humans. A total of 162 patients were exposed to metreleptin for more than 24 weeks.

7.2.2 Explorations for Dose Response

For the 72 patients treated with metreleptin in the NIH pivotal studies, the starting total daily dose ranged from 0.4 mg to 15 mg. Because of the dose titration specified by protocol and subsequent dose adjustments based on individual clinical response, as well as evolution of the dosing regimen over time, a weighted average dose that accounted for the duration of time at a specific dose was calculated as:

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

Weighted average daily doses used up to one year, weighted average daily doses used over the entire study period, and maximum doses used over the study period are summarized in both mg/kg as well as total mg in the following table.

- Mean weighted average daily dose over the entire study period was 6.1 mg (range 0.8 to 19.1 mg) for females and was 2.9 mg (range 0.9 to 6.9 mg) for males.

- Mean weighted average dose up to one year was lower than that over the entire study period and is most likely attributed to lower starting doses followed by dose titration during the initial months of metreleptin treatment.

- As of the 11 Jul 2011 data cutoff, the maximum daily dose of metreleptin administered to any patient ranged from 0.9 mg to 20 mg (0.9 to 20 mg females; 0.9 mg to 10 mg males), with most patients (58 of 72) receiving 10 mg/day or less.

Table 44. Total Daily Doses of Metreleptin by Sex and Generalized versus Partial Lipodystrophy, NIH Trials

		Daily Dose in mg/kg			Daily Dose in mg		
Gender, Diagnosis		Weighted Average up to 1 Year [1]	Weighted Average Over Study Period [2]	Maximum Over Study Period	Weighted Average up to 1 Year [1]	Weighted Average Over Study Period [2]	Maximum Over Study Period
Male, Generalized LD							
(N = 12)	Mean (SE)	0.046 (0.004)	0.053 (0.006)	0.07 (0.01)	2.37 (0.23)	2.93 (0.43)	3.95 (0.66)
	Min, Max	0.03, 0.08	0.03, 0.10	0.04, 0.14	0.9, 4.3	0.9, 6.9	0.9, 10.0
	CV %	33.64	37.49	43.90	32.91	50.95	57.43
Female, Generalized LD							
(N = 36)	Mean (SE)	0.077 (0.005)	0.099 (0.006)	0.12 (0.01)	4.08 (0.49)	5.29 (0.57)	6.57 (0.75)
	Min, Max	0.02, 0.21	0.02, 0.21	0.03, 0.26	0.8, 18.7	0.8, 19.1	0.9, 20.0
	CV %	41.32	36.28	44.94	71.45	64.27	68.74
Female, Partial LD							
(N = 24)	Mean (SE)	0.092 (0.005)	0.117 (0.007)	0.15 (0.01)	5.71 (0.50)	7.27 (0.58)	9.19 (0.86)
	Min, Max	0.06, 0.18	0.07, 0.20	0.08, 0.25	1.0, 11.1	1.0, 13.2	1.2, 20.0
	CV %	27.96	27.69	34.89	43.10	38.75	46.00
All Female Patients							
(N = 60)	Mean (SE)	0.083 (0.004)	0.107 (0.005)	0.13 (0.01)	4.73 (0.37)	6.09 (0.43)	7.62 (0.59)
	Min, Max	0.02, 0.21	0.02, 0.21	0.03, 0.26	0.8, 18.7	0.8, 19.1	0.9, 20.0
	CV %	36.40	33.31	41.18	59.96	54.30	59.79

[1] Average up to one year is weighted by time for each patient according to the formula: Sum[Daily Dose*Duration (Days) of the Dose Regimen]/Total Days of All Dose Regimens, restricted to the first year of dosing.
[2] Average over the entire study period is weighted by time for each patient according to the formula: Sum[Daily Dose*Duration (Days) of the Dose Regimen]/Total Days of All Dose Regimens, over the study period.

Source: Clinical Efficacy Update, Table 7

7.2.3 Special Animal and/or In Vitro Testing

In vitro testing was conducted to assess the neutralizing activity of anti-drug antibodies. The assessment of the adequacy of this evaluation is pending review from the Office of Biotechnology Products.

7.2.4 Routine Clinical Testing

Limitations to assessing the adequacy of routine clinical testing were addressed in Section 3.1, Submission Quality and Integrity. In addition, there were significant limitations to the antibody assessment as discussed in Section 7.4.6, Immunogenicity.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal metabolic, clearance, or interaction assessments were conducted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

Patients Treated for Lipodystrophy

In a published case series of 70 patients with CGL, eight (11%) patients died prematurely between the ages of 19 months and 35 years.[29] It is also notable that deaths in two patients with CGL were reported while awaiting metreleptin treatment in the NIH protocol (one who died at age 30 of sudden cardiac death and another age 31 who died of idiopathic pulmonary fibrosis).[30]

In the NIH trials, as of the 11 July 2011 cutoff, three deaths were reported out of 72 ITT patients: one patient out of 55 in the 31 July 2009 cutoff and two patients between the 2009 and the 2011 cutoffs.

In addition, in the NIH trials, two deaths (31 July 2009 cutoff) occurred several months after discontinuation of metreleptin treatment.

In the FHA101 trial, as of the 07 March 2012 cutoff, two adverse events leading to death were reported out of 28 ITT patients: one patient in the 14 June 2010 cutoff and one patient between the 2010 and 2012 cutoffs.

In the four-month safety update in which an additional 25 patients were enrolled from the previous data cutoffs to the new data cutoff of January 2013 (total N = 125) there was one additional report of death from a patient in the NIH trials (no additional deaths in the FHA101 trial).

Therefore, a total of eight (6.4%) patients enrolled in the lipodystrophy trials up until the January 2013 data cutoff died (N=125);[§§§§§§] six (4.8%) of these patients were on metreleptin therapy or within one month of drug discontinuation at the time of death.

Narratives for these six patients are as follows [discussions of the two deaths that occurred more than one month after discontinuation of metreleptin are discussed with: (1) the serious adverse events in Section 7.3.2 (Patient 90109 hypoalbuminemia, worsening of proteinuria, and worsening of liver disease); and (2) the discussion of malignancies in Section 7.6.1 (Patient 90147 T-cell lymphoma)[§§§§§§]]:

- Renal failure (NIH Trial): At study entry, Patient 90106 was a 35-year-old black female with CGL. Other relevant past medical history at study entry included pneumonia, hyperlipidemia, diabetes, peripheral vascular disease, proteinuria, total knee replacement, hip replacement, a history of smoking, avascular necrosis, and left shoulder pain. The patient experienced a serious adverse event of myoclonus, muscular weakness, and pain in extremity on Day 2 (09 Sep 2000) of metreleptin treatment and a serious adverse event of respiratory distress on Day 13 (20 Sep 2000) of metreleptin treatment. She was treated with metreleptin from 15 Nov 2000 until 16 Jan 2002 when she stopped study medication on 16 Jan 2002 and discontinued study participation. On 29 Aug 2008 (approximately six and half years after discontinuing study participation), the patient resumed study participation at the NIH and restarted metreleptin treatment. She had one follow-up visit at the NIH in May 2009, which was her last visit there. At that time, it was noted that her kidney disease, originally noted in 2000 prior to ever starting study medication, had worsened, as evidenced by her decreasing creatinine clearance. The patient stated she did not desire dialysis and expressed reservation about nephrology follow-up as she did not want dialysis. On (b) (6), the patient's brother called the NIH to report that the patient had died on (b) (6) (approximately one and a half years after restarting metreleptin treatment) from kidney failure. The brother reported that the patient was not feeling well on (b) (6) and went to the local emergency room seeking care. The patient was sent home, but returned (b) (6) as she still was not feeling well. She went into cardiac arrest, and was unable to be resuscitated. The emergency room physician told the family the patient was in kidney failure, went into shock, and was unable to be resuscitated. She received the last dose of study medication on 03 Mar 2010.

[§§§§§§] An additional patient was known to have died 8 months after study discontinuation (Patient 90115, T-cell lymphoma); but this death was not captured in the total because the event leading to death was not reported as an adverse event.

Reviewer comment: It is unclear what the precipitating event was for this patient's death. It is noted that she was sent home from the Emergency Department the day prior to cardiac arrest from reported renal failure.

- Progressive end-stage liver disease (NIH Trial): At study entry, Patient 90158 was an 18-year-old Hispanic female patient with AGL. Relevant past medical history at study entry included severe liver disease with cirrhosis, elevated ammonia levels, constipation, hypercholesterolemia, mild renal insufficiency, proteinuria, diabetes, and pancytopenia. On (b) (6), on Day 346 of treatment with metreleptin, the patient experienced a serious adverse event of hepatic encephalopathy with altered consciousness related to constipation and taking pain medications for the constipation. The event resolved within a few days after receiving lactulose, and she was discharged in good condition. On (b) (6), the NIH was informed that the patient had been in the hospital for a few weeks due to chronic hepatic failure and was placed on life support and died on (b) (6). The final dose of study medication was administered that day. The patient had received approximately 1.4 years of metreleptin treatment at the time of her death. No further information is available.

Reviewer comment: It is not clear if the patient's liver disease was due to non-alcoholic steatohepatitis (NASH) or if she had autoimmune hepatitis (or both). It appears that some patients with AGL also have autoimmune hepatitis. In theory, metreleptin could make an autoimmune disease such as autoimmune hepatitis worse, even if there is an improvement in NASH. However, this is speculative in this case.

- Pancreatitis, septic shock, and cardiac arrest (NIH Trial): At study entry, patient 90125 was a 15-year-old Native American female with CGL. Other relevant past medical history at study entry included history of pancreatitis (further details not available), hypertension, diabetes, focal segmental glomerulosclerosis, and hyperlipidemia (TG 1669 mg/dL at baseline visit 22 Sep 2003). On (b) (6), Day 104 of treatment with metreleptin, the patient was hospitalized with pancreatitis. The patient was diagnosed with a ruptured pseudocyst of the pancreas and subsequently developed septic shock leading to cardiac arrest. The patient was resuscitated and an emergency laparotomy was performed in an attempt to locate a possible ruptured pseudocyst of the pancreas; this was not found. The patient subsequently died on (b) (6) when life support was removed in the absence of brain activity. The patient took metreleptin up to (b) (6) (the day prior to admission for pancreatitis). The investigator noted that according to the patient's local physician, she only took metreleptin 4 to 5 times per week although she should have been taking it 14 times per week. No follow-up study assessments on metreleptin were performed in this patient. It was the investigator's opinion that the

pancreatitis occurred because the patient was not compliant with metreleptin and that the metreleptin should have been tapered.

Reviewer comment: It is unclear what the diagnosis of ruptured pseudocyst was based on, considering that a laparotomy was apparently unrevealing.

- Progressive adenocarcinoma (FHA101 Trial): At study entry, patient 649001 was a 67-year-old white female with AGL. Relevant medical history included adenocarcinoma of undetermined origin, ascites, and esophageal reflux.******* On (b) (6) (b) (6), approximately 79 days after starting treatment with metreleptin, the patient experienced emesis, with blood noted, and an acute exacerbation of abdominal pain. It was unclear if the patient had a previous history of abdominal pain, but had been taking Zantac as needed for symptoms of reflux. Her metreleptin was temporarily stopped on (b) (6). The patient was admitted to the hospital and underwent an abdominal computerized tomography scan on (b) (6) which revealed rounded calcified deposits in the pelvis and faint calcifications over the liver dome, likely from mucinous adenocarcinoma metastases, mild hypertrophy of the left liver lobe, and bilateral pleural effusions. An upper gastrointestinal endoscopy was performed on (b) (6), which was consistent with severe erosive esophagitis. A small bowel series performed on (b) (6) demonstrated subjectively delayed gastric emptying. On the same day, the patient underwent paracentesis, at which time 3200 mL of amber fluid was removed. The patient was treated with intravenous Nexium and Zofran. She was started on total parenteral nutrition (TPN) and had a peripherally inserted central catheter placed. The patient was discharged home on (b) (6), and the event of erosive esophagitis was considered by the investigator as resolved on that day. Additional information was received from the investigator on 27 Sep 2010, which indicated that the events of the prior hospitalization were consistent with progressive adenocarcinoma of undetermined origin (onset date o (b) (6)), complicated by a small bowel obstruction. The patient had a Do Not Resuscitate order and she died on (b) (6) (b) (6) She had not resumed metreleptin treatment after stopping on (b) (6).

Reviewer comment: Because this patient was enrolled in the simplified protocol in the FHA101 trial, not much information was provided about this patient's medical history or condition at the start of the trial (i.e., it was not reported whether her illness was presumed to be terminal at the time she was enrolled in the trial). This appears to be a fairly rapid progression of her disease. It is unknown if metreleptin could have contributed to the worsening of the adenocarcinoma (i.e, as a tumor promotor).

******* Additional relevant past medical history that apparently was not captured in the database but reported in the Clinical Safety Update included cutaneous T-cell lymphoma (mycosis fungoides) diagnosed in 1981 that resolved with natural therapies. Note that because this patient was enrolled in a simplified protocol, information regarding medical history was not provided in the case report form.

- Loss of consciousness (FHA101 Trial): At study entry, patient 648008 was a 67-year-old white female with APL. Relevant medical history at study entry included diabetes since age 10, gastroparesis, high triglycerides since age 10, high cholesterol, hypertension, fatty liver, increased LFTs, coronary artery disease, s/p two cardiac stents in 2006, peripheral vascular disease, s/p axillofemoral bypass in 2006, autoimmune overlap syndrome (rheumatoid arthritis and systemic lupus erythematosis), autoimmune retinitis, hypothyroidism, anxiety, seizures in 2009, and history of smoking (one pack per day for more than 30 years). On (b) (6), day 51 of treatment with metreleptin, the patient tripped and fell in her home. She was known to have hit her head in the fall and was seen by her primary care physician and was deemed to be alright. The patient had three uneventful days. On (b) (6) (b) (6), she complained of fatigue and was noted to have a cough (which had begun approximately three weeks prior). On (b) (6), day 56 of treatment with metreleptin, the patient told her son that she felt hot, skipped dinner, and went to bed at approximately 6 pm. At 10 pm, the patient awoke, used the restroom and when she came out experienced weakness, confusion, and became unresponsive and lost consciousness. Her son noted that she seemed to be having a seizure. She was resuscitated by EMS after approximately 10-20 minutes. Evaluation in the ICU over the next several days suggested that her prognosis for neurologic recovery was very poor. A CT of the head (b) (6) revealed acute bilateral tentorial subdural hematoma. The decision to discontinue invasive supportive care was made and the patient died on (b) (6). No autopsy was conducted.

- Anoxic encephalopathy (NIH Trial): At study entry (16 Dec 2008), patient 90151 was a 27-year-old white female with a history of FPL. Relevant past medical history at study entry included type 2 diabetes mellitus, hypertriglyceridemia, hypertension, atrial septal defect, non-alcoholic steatohepatitis, recurrent pancreatitis, acute renal failure, asthma, sleep apnea, gastroparesis, gastroesophageal reflux disease, chronic cholecystitis, neuropathy, depression, insomnia, obsessive-compulsive disorder, tobacco use, and multiple allergies (codeine, morphine, oxycodone, sulfamethoxazole and latex). Recent serious adverse events prior to this event included severe abdominal pain in July 2011, lower gastrointestinal hemorrhage in October 2011, and ovarian dermoid cyst in November 2011. On (b) (6), after approximately 3.4 years of treatment with metreleptin, the patient's mother found her unconscious in her apartment. The patient was admitted to the Intensive Care Unit of a local hospital and diagnosed with anoxic encephalopathy. Metreleptin therapy was interrupted upon admission (last dose on (b) (6)). The patient never regained consciousness, and died on (b) (6) under hospice care. The death certificate listed the cause of death as anoxic encephalopathy, with diabetes mellitus, hypertension, and Dunnigan-Kobberling syndrome as underlying conditions leading to death, and chronic pancreatitis, sleep apnea and seizures as other significant conditions contributing to death. Tobacco use was also listed as probably contributing to death. Per the site, seizures reported on the death certificate most

likely occurred during the patient's hospitalization. No further information was provided. An autopsy was not performed.

The following table lists the eight deaths in the lipodystrophy trials, including the two patients (90109, 90147) who died after trial discontinuation. §§§§§§

Table 45. Deaths in the Lipodystrophy Trials: NIH and FHA101

Trial	Cutoff date	Patient	Age / sex / lipodystrophy type	Past medical history	Cause of death	Duration of metreleptin therapy
NIH	31 Jul 2009	90125	15 yo / F / CGL	Pancreatitis, hypertension, diabetes, focal segmental glomerulosclerosis, and hyperlipidemia (BL TG 1669 mg/dL)	Pancreatitis, subsequent septic shock leading to cardiac arrest	104 days
NIH	31 Jul 2009	90147	59 yo / F / AGL	Severe neutropenia, abnormal bone marrow, lipoatrophic diabetes, history of benign breast fibroma, non-alcoholic steatohepatitis	Multisystem organ failure related to peripheral T-cell lymphoma	242 days
NIH	31 Jul 2009	90109	13 yo / F / AGL	Steatohepatitis with bridging f brosis, membranoproliferative glomerulonephritis	Hepatorenal failure	444 days
NIH	11 Jul 2011	90106	35 yo / F / CGL	Pneumonia, hyperlipidemia, diabetes, peripheral vascular disease, proteinuria, total knee replacement, hip replacement, history of smoking, avascular necrosis, and left shoulder pain	Renal failure leading to cardiac arrest	428 days (first treatment) 554 days (second treatment)
NIH	11 Jul 2011	90158	18 yo / F / AGL	Severe liver disease with cirrhosis, elevated ammonia levels, constipation, hypercholesterolemia, mild renal insufficiency, proteinuria, diabetes, and pancytopenia	Chronic hepatic failure leading to death	526 days
NIH	After 11 Jul 2011	90151	27 yo / F / FPL	Chronic cholecystitis, type 2 diabetes, hepatosteatosis, hypertriglyceridemia, hypertension, atrial septal defect, depression, sleep apnea, gastroparesis, gastroesophageal reflux disease, insomnia, recurrent pancreatitis, obsessive compulsive disorder, tobacco user, and multiple allergies††††††	Anoxic encephalopathy (found unconscious)	1232 days
FHA101	14 Jun 2010	648008	67 yo / F / APL	Diabetes, gastroparesis, hypertriglyceridemia, high cholesterol, hypertension, fatty liver, increased LFTs, coronary artery disease s/p 2 cardiac stents, peripheral vascular disease s/p axillofemoral bypass, autoimmune overlap syndrome, autoimmune retinitis, hypothyroidism, anxiety, seizures, history of smoking	Loss of consciousness	56 days
FHA101	07 Mar 2012	649001	67 yo / F / AGL	Adenocarcinoma of undetermined origin, ascites, and esophageal reflux	Progressive adenocarcinoma	79 days

Source: BLA 125390, Clinical Safety Update (27 Mar 2013 submission); NIH adverse event listings; FHA101 adverse event listings; Summary of Clinical Safety

†††††† The case report form also reported past medical history of motor and sensory neuropathy, diabetic retinopathy, asthma, and acute renal failure

Patients Treated for Obesity

In the five Amgen obesity trials (LEPT-970164, LEPT-970213, LEPT-980236, LEPT-970188, and LEPT-970171) summarized in the integrated summary of safety (ISS), 1072 obese patients received at least one dose of randomized study medication (metreleptin or placebo). Of these patients, 784 received metreleptin and 351 received placebo.

One patient died after a diagnosis of lymphocytic leukemia approximately one month after initiating metreleptin 20 mg.

- Lymphocytic leukemia (LEPT-980236 Trial): Patient 1203 was a 67-year-old female with a medical history of obesity, on the following concomitant medications: ethinylestradiol, multivitamins, calcium, and Ascripton (Maalox-buffered aspirin). On study day 29, she was hospitalized with pneumonia and study drug was discontinued. Her WBC was 104,160 cmm, neutrophils 2%, and lymphocytes 95%. A diagnosis of lymphocytic leukemia was made. She was treated with antibiotics and chemotherapy and was discharged from the hospital to hospice care. She died 30 days later.

Reviewer comment: Of note, the patient's screening (day -5) and baseline (day 1) WBC was approximately 5 x10^9/L. Her baseline lymphocytes were 80% and baseline neutrophils were 17% (absolute neutrophil count approximately 850). No further information about this patient's medical history was provided. The confounding factor of baseline neutropenia as well as the fact that the patient was only exposed to metreleptin for one month makes it difficult to attribute the event to metreleptin.

No deaths were reported in Amgen studies LEPT-960176, LEPT-960240, LEPT-970161 (congenital leptin deficiency), LEPT-970211, LEPT-980145, LEPT-980219, and LEPT-980225; as well as Amylin studies DFA101, DFA102, and DFA102E. No deaths were reported during DFA104; however, one death in a patient randomized to placebo occurred after the completion of the trial, as described here:

- Lymphangitic adenocarcinoma of the lung (DFA104 Trial, post-completion): Patient 109001 was a 60-year-old white female with a medical history of obesity (BMI 43.4 kg/m^2), hyperthyroidism, overactive bladder, bilateral varicose veins, hypertension, sinus infection, and persistent cough, who was diagnosed with lymphangitic adenocarcinoma of the lung 36 days after the first dose of randomized study medication and 23 days after the last dose of study medication. The patient's symptoms progressed at an "alarming" rate with increased cough, dyspnea, and hypoxia. The patient received morphine for cough and dyspnea and was treated with paclitaxel and carboplatin. The patient continued to deteriorate with obvious respiratory failure and died approximately 40 days after the last study dose.

Reviewer comment: Both cancer deaths in the obesity trials occurred in patients with abnormal baseline findings that were likely evidence of pre-existing disease.

7.3.2 Nonfatal Serious Adverse Events

Patients Treated for Lipodystrophy

As of the 11 Jul 2011 data cutoff, 17 (24%) of 72 ITT patients in the NIH trials experienced a total of 40 serious adverse events, including three fatal events. The System Organ Classes with the most frequently reported serious adverse events were *Gastrointestinal Disorders* (five [6.9%] patients, including four patients with pancreatitis, one of whom also had colitis, and one patient with abdominal pain) and *Infections and Infestations* (six [8.3%] patients, including two patients with appendicitis, one patient with cellulitis, pharyngitis, and streptococcal infection, one patient with pneumonia parainfluenza viral, one patient with pneumonia, and one patient with septic shock in the setting of acute pancreatitis, described in Section 7.3.1, Deaths, above). In the four-month safety update (data cutoff 11 Jan 2013), 25 of 90 patients (27.8%) experienced a total of 58 serious adverse events, including the events from the previous data cutoff.

In the FHA101 trial, as of 07 Mar 2012, 9 (32.1%) of 28 patients experienced a total of 18 serious adverse events, including two fatal events. In the four-month safety update (data cutoff 09 Jan 2013), 10 (28.6%) of 35 patients experienced a total of 27 serious adverse events, including the events from the previous data cutoff.

The table below lists all serious adverse events in the lipodystrophy trials, up until the final data cutoffs in the four-month safety update.

Table 46. Treatment-Emergent Serious Adverse Events [NIH trials 991265 / 20010769, data cutoff 11 Jan 2013, and FHA101, data cutoff 09 Jan 2013]

Trial	Patient ID Age / Sex / Lipodystrophy Type	Relevant Medical History	Preferred Term [1]	Time to Onset (Days)	Outcome
NIH	90101 17 / F / AGL	Pancreatitis, hypertriglyceridemia (TG 7420 mg/dL), xanthoma	Pancreatitis	4084	Recovered/Resolved
			Superior mesenteric artery syndrome	4084	Recovered/Resolved
NIH	90103 27 / F / AGL	Autoimmune hepatitis, liver f brosis, depression	Hepatic enzyme increased	481	Recovered/Resolved
			Paranoia	655	Recovered/Resolved
NIH	90105 14 / F / CGL	Hypertension (baseline BP 149/85), tachycardia (baseline HR 105), nonalcoholic steatohepatitis, proteinuria	Hypertension	0 [2]	Recovered/Resolved
NIH	90106 35 / F / CGL	Peripheral vascular disease, amputated left great toe, diabetes mellitus, deep vein	Muscular weakness	1	Recovered/Resolved
			Myoclonus	1	Recovered/Resolved
			Pain in extremity	1	Recovered/Resolved
			Respiratory distress	12	Recovered/Resolved

		thrombosis, lower extremity weakness, avascular necrosis, left shoulder pain, smoking, proteinuria (2.6 g/24 h)	Renal failure	3464	Fatal
NIH	90107 42 / F / FPL	Focal glomerulonephritis, stage IV kidney failure, proteinuria (1.9 g/24 h), coronary artery disease, multiple stent placements, stable angina, hypertension, hypertriglyceridemia, diabetes mellitus, recurrent pancreatitis	Right renal transplant	2748	Recovered/Resolved
			Cellulitits	106	Recovered/Resolved
			Pharyngitis	106	Recovered/Resolved
			Streptococcal infection	106	Recovered/Resolved
			Catheterization cardiac	2657	Recovered/Resolved
NIH	90109 13 / F / AGL	Diabetes, nonalcoholic steatohepatitis, bridging f brosis, multiple episodes of pancreatitis, proteinuria (2.7 g/24 h), hypertriglyceridemia, xanthoma	Hypoa buminaemia	422	Not reported
			Liver disorder	422	Not reported
			Proteinuria	422	Ongoing [3]
			Pancreatitis	168	Recovered/Resolved
NIH	90110 8 / F / AGL	Asthma, frequent upper respiratory infections, IgA deficiency, Kawasaki's disease, allergic rhinitis, autoimmune hepatitis, mild portal fibrosis, fatty liver, diabetes mellitus, mild proteinuria	Alanine aminotransferase increased	34	Recovered/Resolved
			Chest discomfort	194	Recovered/Resolved
			Dyspnea	194	Recovered/Resolved
			Flushing	194	Recovered/Resolved
			Panic reaction	194	Recovered/Resolved
			Pneumonia parainfluenzae viral	1021	Recovered/Resolved
NIH	90116 47 / F / CGL	Diabetes mellitus, hyperlipidemia, chronic kidney disease, renal transplant, pancreatitis, hepatic steatosis, hepatitis, cirrhosis, celiac disease	Lower gastrointestinal hemorrhage	3566	Recovered/Resolved
NIH	90121 32 / F / FPL	Pancreatitis, hypertriglyceridemia, diabetes mellitus, xanthoma, chronic abdominal pain	Pancreatitis	43	Recovered/Resolved
NIH	90125 15 / F / CGL	Pancreatitis, hypertension, baseline TG 1669 mg/dL, focal segmental glomerulosclerosis	Cardiac arrest	106	Fatal
			Pancreatitis	104	Fatal
			Septic shock	104	Fatal
NIH	90128 15 / M / AGL	Diabetes mellitus, hypertriglyceridemia, severe depression, chronic abdominal pain, nausea, vomiting, dehydration, autoimmune hepatitis, chronic transaminasemia	Abdominal pain	2032	Ongoing [4]
			Dehydration	2032	Ongoing [4]
NIH	90135 35 / F / FPL	Diabetes mellitus, benign ovarian masses, pancreatitis (recurrent severe)	Appendicitis	39	Recovered/Resolved
			Ovarian cysts	90	Recovered/Resolved
NIH	90136 23 / F / FPL	Depression (severe), attempted suicide (past suicide attempts as teenager; mother committed suicide at age 31), history of abuse and neglect as a child, adjustment disorder	Suicide attempt	~1431	Recovered/Resolved

NIH	90137 13 / F / CGL	Diabetes mellitus, pancreatitis, hypertriglyceridemia, depression, hypertension, left ventricular hypertrophy	Appendicitis	~925	Recovered/Resolved
NIH	90138 34 / F / FPL	Lipoatrophic diabetes, pancreatitis, nonalcoholic steatohepatitis, hypertriglyceridemia (TG 359 mg/dL)	Colitis	874	Recovered/Resolved
			Pancreatitis	876	Recovered/Resolved
NIH	90143 13 / F / CGL	Insulin resistance (2005), diabetes mellitus, non-alcoholic steatohepatitis, cirrhosis, hepatopulmonary syndrome	Sepsis [5]	~1497	Recovered/Resolved
NIH	90147 59 / F / AGL	Intermittent neutropenia, hepatosplenomegaly, multinodular goiter, thyroidectomy	T-cell lymphoma	233	Withdrawn from study
NIH	90151 27 / F / FPL	Diabetes, severe hypertriglyceridemia, xanthomas, hepatosteatosis, acute renal failure, pancreatitis, intermittent diarrhea, gastroparesis, chronic cholecystitis	Abdominal pain	947	Recovered/Resolved
			Ovarian germ cell teratoma	1064	Recovered/Resolved
			Lower gastrointestinal hemorrhage with anaemia	1030	Recovered/Resolved
			Anoxic encephalopathy (fatal)	1232	Fatal
NIH	90156 22 / F / CGL	Hashimoto's thyroiditis, acromegaly of the hands, severe insulin resistance, hypertriglyceridemia, vitamin D deficiency, pancreatitis, papillary thyroid cancer	Thyroid cancer	705	Recovered/Resolved
			Premature baby Maternal exposure during pregnancy	1274	Recovered/Resolved
NIH	90158 18 / F / AGL	Severe liver disease with cirrhosis, diabetes mellitus, hypercholesterolemia, mild renal insufficiency, proteinuria	Hepatic encephalopathy	344	Recovered/Resolved
			Chronic hepatic failure	523	Fatal
NIH	90164 16 / F / CGL	Cirrhosis, chronic gastritis, grade III esophageal varices, hepatic encephalopathy, diabetes with extreme insulin resistance, hypertriglyceridemia, IgA nephropathy, proteinuria, hypertension	Liver disorder (Hepatic encephalopathy)	807	Recovered/Resolved
			Liver disorder	874	Recovered/Resolved
			Abdominal pain	858	Recovered/Resolved
NIH	90168 1 / M / CGL	Viral syndrome, hypertension, hypertriglyceridemia, fatty liver, hepatomegaly	Pneumonia	98	Recovered/Resolved
NIH	90170 11 / F / AGL	Non-alcoholic steatohepatitis, hyperlipidemia, hypertriglyceridemia, severe insulin resistance	T-cell lymphoma	659	Ongoing
NIH	90180 28 / F / FPL	Chronic pancreatitis (usually in conjunction with hypertriglyceridemia of 500-14,000), extreme insulin resistance with type 2 diabetes, diabetic ketoacidosis, chronic pain disorder with opioid use	Abdominal pain (Pancreatitis chronic?)	20	Recovered/Resolved
			Abdominal pain (Pancreatitis chronic?)	108	Recovered/Resolved
			Abdominal pain	197	Recovered/Resolved

FHA101	648001 9 / F / AGL	History of acute pancreatitis, high triglycerides (10,623 mg/dL), diabetes mellitus	Pancreatitis acute	191	Recovered/Resolved
			Constipation	942	Recovered/Resolved
			Pancreatitis (with ileus)	1205	Recovering
			Diabetic ketoacidosis	1205	Recovered/Resolved
			Hypertriglyceridemia	1311	Recovering
			Hyperglycemia	1305	Recovering
FHA101	648003 58 / F / FPL	Coronary artery disease, hypertension, CABG, GERD, fatty liver, back and neck pain, lipid abnormalities, diabetes, hyperthyroidism	Chest pain	500	Recovered/Resolved
FHA101	648004 30 / F / FPL	Diabetes mellitus, hypertension, high triglycerides, fatty liver	Cellulitis	316	Recovered/Resolved
FHA101	648005 50 / F / FPL	Urinary tract infections, diabetes mellitus, hypertriglyceridemia, hypertension	Escherichia urinary tract infection	79	Recovered/Resolved
			Urinary tract infection	446	Recovered/Resolved
			Gastroenteritis	665	Recovered/Resolved
			Hypoglycemia	1157	Recovered/Resolved
			Hypotension	1156	Recovered/Resolved
			Migraine	1151	Recovered/Resolved
			Gastroenteritis	1032	Recovered/Resolved
FHA101	648008 67 / F / APL	Seizures, hypertension, coronary artery disease, two stents, peripheral vascular disease, axillofemoral bypass	Loss of consciousness	56	Fatal
FHA101	648015 62 / F / FPL	Still's disease, type 2 diabetes mellitus, atrial f brillation, aortic atherosclerosis, CVA, acute renal failure, hypertension, lung cancer	Still's disease exacerbation	660	Recovered/Resolved
FHA101	648021 43 / F / FPL	Vertigo intermittent, myopathy, f bromyalgia, hypertension, muscle spasms, Tarui disorder (phosphofructokinase deficiency)	Vertigo positional	80	Recovered/Resolved
FHA101	649001 67 / F / AGL	Ascites, esophageal reflux, adenocarcinoma of undetermined origin	Erosive esophagitis	79	Recovered/Resolved
			Adenocarcinoma	79	Fatal
FHA101	677001 47 / F / FPL	Hyperlipidemia, hypertension, coronary artery disease, peripheral arterial disease, osteomyelitis, iron deficiency anemia	Hypoglycemia	23	Recovered/Resolved
FHA101	677002 25 / F / CGL	Diabetes mellitus, gastroparesis, cirrhosis of liver, recurrent nausea and vomiting, insulin resistance, hypertriglyceridemia, polycystic ovary, retinopathy, microalbuminuria, hypertension, diabetic neuropathy, depression	Abdominal pain	1	Recovered/Resolved
			Nausea	1	Recovered/Resolved
			Vomiting	1	Recovered/Resolved
			Diabetic gastroparesis	210	Recovered/Resolved
			Ileus	209	Recovered/Resolved
			Suicidal ideation	192	Recovered/Resolved

[1] coded using MedDRA v 13.0
[2] Event occurred after first injection of metreleptin treatment.
[3] This SAE was ongoing as of the cutoff date (31 July 2009) for the original BLA submission. Patient 90109 subsequently died of hepatorenal failure about 9 months after cessation of metreleptin treatment.

[4] The patient was hospitalized for the concurrent events, but hospital records were not available and thus, further details, including outcome, are not available. The patient was discharged from the hospital and continued participation in the study as of 11 July 2011.
[5] Reportedly no source of infection was found. Limited information was available from this hospitalization (occurred in home country of Peru).

Source: BLA 125390; Clinical Safety Update submission 27 Mar 2013, Tables 19, 20, 35, and 36

Serious Adverse Events Assessed as Related by the Investigator to Metreleptin

Two serious adverse events in the NIH trials were assessed by the investigator as related to metreleptin treatment: hypertension in Patient 90105, and respiratory distress in Patient 90106.

- The serious adverse event of hypertension and related adverse event (non-serious) of tachycardia occurred in Patient 90105, a 14-year-old patient with CGL and a history of hypertension and tachycardia at baseline. The elevation in blood pressure (195/110 mmHg) occurred after the second dose of metreleptin and was transient, with blood pressure improving to close to baseline levels (170/80 to 90 mmHg) within 15 to 20 minutes; nevertheless, the patient was hospitalized for further monitoring and evaluation. The event was assessed by the investigator as related to metreleptin, likely because of the temporal relationship to the drug administration. The event of hypertension resolved within a few days, and the patient's blood pressure improved (121/69 mmHg) over the next several months after resuming metreleptin treatment and with adjustment of blood pressure medications.

Reviewer comment: The need for adjustment in blood pressure medications is noted. The relationship to metreleptin is unclear.

- The serious adverse event of respiratory distress occurred in Patient 90106, a 35-year-old patient with CGL who had a complicated on and off therapy course due to adverse events at the beginning of metreleptin treatment and experienced an episode of respiratory distress that required hospitalization one day after restarting metreleptin for the third time. The event resolved within one day and the patient continued on therapy for another 14 months.

Two serious adverse events in FHA101 were assessed as related to treatment; both hypoglycemia events.[‡‡‡‡‡‡‡]

- At study entry, Patient 677001 was a 47-year-old white female with FPL. Relevant medical history included diabetes mellitus for 25 years (treated with U-500 insulin without prior history of problems with hypoglycemia; blood glucose values prior to starting metreleptin were in the 200-300's), hyperlipidemia, hypertension, coronary artery disease, peripheral arterial disease, osteomyelitis, and iron deficiency anemia. On 31 Mar 2011, three weeks after starting metreleptin, the patient experienced low

[‡‡‡‡‡‡‡] The event in Patient 648005 was reclassified as "unrelated" by the investigator; however, the event is captured here for completeness.

blood glucose levels with some values being below 60 mg/dL. The patient was taking 75 units of insulin twice daily. On 01 Apr 2011, approximately 23 days after initiating metreleptin treatment, the patient experienced an event of assisted hypoglycemia. The patient was feeling hot and sweaty prior to the event. She was talking on the telephone with her brother when her speech was noted to be slurred and her brother could not understand her. The patient's neighbor, a physician's assistant, was called and found the patient in bed. The neighbor was able to arouse her, but the patient was clammy, diaphoretic and appeared tired. The neighbor reported that the patient was able to answer questions and did not appear to be postictal or have lost bowel or bladder function. No head or body contusions were noted, and it did not appear that the patient had fallen. The patient was given sips of oral carbohydrate (Pepsi); blood glucose level by finger stick 5 to 6 minutes afterwards was apparently 137 mg/dL. The patient's mental status and level of alertness appeared to improve significantly after ingestion of oral carbohydrate. The patient stabilized and did not go to the emergency room or hospital. The outcome of assisted hypoglycemia resolved on the same day. The investigator confirmed that the patient took metreleptin on the date she experienced the event. The patient continued in the trial.

- At study entry, Patient 648005 was a 50-year-old white female with FPL. Relevant medical history included hypertension, type 2 diabetes, hypothyroidism, hypercholesterolemia, hypertriglyceridemia, fatty liver, recurrent urinary tract infections, proteinuria, weakness, neuropathy, acanthosis nigricans, recurrent folliculitis, nocturia, and chronic leukocytosis. Relevant recent medical history included a hospitalization on (b) (6) for headache (migraine) and hypertensive urgency. The patient received intravenous labetalol, analgesics and compazine with improvement, and was discharged on (b) (6) with a blood pressure of 103/64 mmHg, and prescriptions for topiramate and prochlorperazine. On (b) (6), approximately 1155 days after initiating metreleptin therapy, the patient began to feel dizzy and “not with it”. Her blood pressure was 82/60 mmHg. She received intravenous fluids in the emergency room and was admitted to the hospital for observation due to refractory hypotension. The provisional diagnosis was hypotension, potentially due to a drug interaction, topiramate causing hypotension, dehydration, or medication as etiology with a thiazide diuretic. The patient’s topiramate was discontinued, and blood pressure medications were adjusted. The patient’s blood pressure improved. On (b) (6), while still hospitalized, the patient experienced a low blood sugar of 36 mg/dL at 11 pm, feeling very foggy and very unstable. She received oral carbohydrates and the hypoglycemia was reported resolved that same day. This event occurred after topiramate was discontinued, and was felt to have possibly been precipitated by the patient’s nausea or her diabetes medications, including insulin, metreleptin and metformin. The patient was discharged on (b) (6). She remained in the trial as of 09 Jan 2013.

Other Serious Adverse Events of Interest

Other serious adverse events of interest include the following (with the exception of serious adverse events of pancreatitis, which are presented separately in Section 7.3.5, Submission Specific Primary Safety Concerns, and serious adverse events of cancer, which are presented separately in Section 7.6.1, Human Carcinogenicity):

- Increased liver enzyme: At study entry, Patient 90103 (NIH Trial) was a 28-year-old white female with a 23-year history of AGL. Other relevant past medical history at study entry included diabetes, autoimmune hepatitis, liver fibrosis, and hepatosplenomegaly. At the baseline visit on 21 Aug 2000, ALT and AST were 128 and 57 U/L, respectively. Subsequent LFTs during treatment were: 84 and 40 U/L, respectively on 02 Oct 2000, 54 and 34 U/L, respectively on 14 Nov 2000, 44 and 29 U/L, respectively on 16 Jan 2001, 51 and 30 U/L, respectively on 26 Mar 2001, 124 and 75 U/L, respectively on 08 Jun 2001, 51 and 41 U/L, respectively on 29 Aug 2001, 44 and 32 U/L, respectively on 11 Oct 2001. On 28 Dec 2001, day 482 of treatment with metreleptin, the patient experienced an adverse event of increased hepatic enzymes (428 U/L). Details as to whether the elevation of 428 U/L occurred in AST or ALT are not available. The patient was not hospitalized and the adverse event was not considered life threatening but was classified as a serious adverse event due to it being an "important medical event". Metreleptin treatment was stopped on 04 Jan 2002 due to this event. The event of increased hepatic enzymes was assessed as resolved after 12 days on 09 Jan 2002. On the patient's last follow-up visit on 15 Jan 2002, ALT was 272 U/L and AST was 155 U/L. The patient resumed study medication on 14 Mar 2002 and continued treatment until 21 Jun 2002 when she was withdrawn from the study after she experienced an event of paranoia (admitted to a psychiatric hospital for "strange behavior" and "listening to voices"; diagnosed with paranoid delusions and bipolar disorder).

Reviewer comment: This is considered an event of interest because there seems to be a number of patients with AGL and baseline liver disease / autoimmune hepatitis who have liver events. The psychiatric adverse events are noted as well; see further discussion of psychiatric events in Section 7.3.5, Submission Specific Primary Safety Concerns.

- Pregnancy: At study entry, Patient 90105 (NIH Trial) was a 14-year-old white female with CGL and relevant medical history of tachycardia, non-alcoholic steatohepatitis, diabetes, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, proteinuria, and hypertension. The patient experienced a serious adverse event of worsening hypertension in Sep 2000, as described previously. On 13 Apr 2009, after approximately 7.5 years of metreleptin treatment, the patient received confirmation of pregnancy (date of last menstrual period was unknown). At that time, the gestational age was eight weeks with an estimated date of delivery of 25 Nov 2009. The method of contraception at the time of conception was condoms. No adverse

events had been reported. After thorough consideration of the benefits versus risks to both the mother and fetus, the investigator consulted with the patient and her mother and the decision was made to continue metreleptin therapy and study participation. Additional information received from the investigator on 15 Jul 2009 indicated that the patient remained metabolically stable and the pregnancy was uneventful to that point. The patient initiated Novorapid insulin 75 units daily on 06 Aug 2009 and had titrated to 180 units of insulin daily by 10 Oct 2009. On 30 Oct 2009 (37 weeks of gestation), the patient was gaining the appropriate amount of weight and required 180 units of insulin a day to maintain her target blood glucose. On (b) (6), the patient delivered a 9.5 pound, 22 inch male infant via vaginal delivery. Novorapid was discontinued upon delivery. An episiotomy was performed, which was not considered by the investigator to be an adverse event. The baby was born as a stillbirth with Apgars of 0 and 0, but was successfully resuscitated after full code efforts. After delivery, it was noted that the infant had weakness and limitation of movement of his left arm. The infant was transferred to the NICU and later diagnosed with shoulder dystocia and Erb's palsy. The patient continued metreleptin therapy, began breastfeeding the infant, and continued to breastfeed until 01 Apr 2010. The infant underwent physical therapy with improvement and increased strength of the left arm. At the time of the last follow-up information from the investigator, the infant was a healthy and well-developing 5-month-old with improving Erb's palsy. The stillbirth and shoulder dystocia were assessed as secondary to the vaginal delivery, large for gestational age (from maternal gestational diabetes), and had become caught in the birth canal with resultant traumatic birth injury. Of note, the infant had drug exposure during pregnancy as well as via breast milk.

- Chronic renal failure: At study entry, Patient 90107 (NIH Trial) was a 42-year-old white female with FPL. Other relevant past medical history at study entry included focal glomerulonephritis, proteinuria, stage 4 kidney failure since 1999, hypertension, hypertriglyceridemia, hepatomegaly, and diabetes mellitus. At baseline, the patient's serum creatinine was 1.6 mg/dL (27 Nov 2000). On 03 Dec 2000, 24-hr urine protein was 1891.7 mg. The patient's serum creatinine ranged from 1.3 to 2.1 mg/dL through year 3 of treatment. Between three to five years of treatment, serum creatinine ranged from 2.3 to 2.7 mg/dL. On 13 Nov 2006 (month 68 of metreleptin treatment), serum creatinine was 4.7 mg/dL. Twenty-four hour urine protein results were 2208 mg, 1840 mg, 2252 mg, 739 mg, 473 mg, at years 1, 2, 3, 4, and 5, respectively and 819 mg on 14 Nov 2006. In Nov 2007, the patient developed end-stage renal disease requiring peritoneal dialysis. On (b) (6), after approximately 7.5 years of metreleptin treatment, the patient underwent a right renal transplant. The patient continued taking metreleptin and participating in the study following the renal transplant.

- Hypoalbuminemia, worsening of proteinuria, and worsening of liver disease: At study entry, Patient 90109 (NIH Trial) was a 13-year-old white female with a seven-

year history of AGL. Relevant past medical history at study entry included type 1 diabetes, polyuria, hypertriglyceridemia, hepatomegaly, bridging fibrosis, non-alcoholic steatohepatitis, pancreatitis, proteinuria, and albuminuria. The patient initiated treatment with metreleptin on (b) (6). This patient also experienced a serious adverse event of pancreatitis on 25 Feb 2002 (see the description of the event in Section 7.3.5, Submission Specific Primary Safety Concerns). At baseline on 04 Sep 2001, the patient's ALT and AST were 79 U/L and 85 U/L, respectively, with an albumin of 3.8 g/dL and total bilirubin of 0.2 mg/dL. During the first year of metreleptin treatment, ALT ranged from 75 to 185 U/L, AST ranged from 110 to 190 U/L, albumin ranged from 3.4 to 4.4 g/dL, and total bilirubin ranged from 0.3 to 1.2 mg/dL. On 26 Sep 2002, ALT rose to 445 U/L and AST to 479 U/L while albumin decreased to 2.6 g/dL and total bilirubin remained stable at 0.7 mg/dL. On (b) (6) (b) (6), after 424 days of treatment with metreleptin, the patient had a marked elevation in liver enzymes (AST 1159 U/L and ALT 300 U/L) with low serum albumin (1 g/dL) and rising total bilirubin (2 mg/dL). The patient was admitted to the hospital. She was noted to have massive proteinuria (24-hr protein excretion of 20 g) compared to baseline 24-hr urine protein excretion which ranged between 2-4 g per day. An adverse event of membranoproliferative glomerulonephritis (MPGN) was reported on (b) (6). The patient was treated with human albumin, furosemide, metolazone, lisinopril, spironolactone, and vitamin K. Within several days of admission, the liver abnormalities improved whereas the proteinuria continued. The patient was also diagnosed with alpha hemolytic streptococcal infection during this admission and received ceftriaxone treatment. The events of hypoalbuminemia and worsening proteinuria and liver disease were attributed to the patient's underlying kidney and liver disease. Pioglitazone therapy had been discontinued 30 Oct 2002 and was not restarted. Metreleptin was discontinued on 27 Nov 2002, and the patient was withdrawn from the study on 02 Dec 2002. The event of proteinuria had not resolved by 02 Dec 2002. Per follow up information received from the investigator on 15 May 2007, the patient died due to hepatorenal failure nine months after stopping metreleptin therapy (exact date not provided). The patient apparently needed both a kidney and a liver transplant, but was never officially placed on a transplant list.

Reviewer comment: As described in Section 7.3.3, Dropouts and/or Discontinuations, this patient was discontinued from the trial due to "health issues" (not considered an adverse event). No details were provided regarding the diagnosis of MPGN (i.e., renal biopsy). As noted in a 2004 NIH publication that described this patient's case, it is possible that metreleptin could have exacerbated MPGN this patient.[30] Notably, she had AGL, an autoimmune condition. The cause for the acute rise in transaminases in this patient is unknown.

- Alanine aminotransferase increased: At study entry, Patient 90110 (NIH Trial) was an 8-year-old white female with a two year history of AGL. Other relevant past

medical history at study entry included hepatosplenomegaly, mild portal fibrosis and regenerative hyperplasia in liver, fatty liver, autoimmune hepatitis, hypertriglyceridemia, Hashimoto thyroiditis, Kawaski's disease, and type 2 diabetes.[§§§§§§§] At Visit 1 on 27 Nov 2001, the patient's ALT was 53 U/L and AST was 39 U/L. On 02 Jan 2002, day 35 of treatment with metreleptin, the patient experienced an increased ALT of 230 U/L. Two days later, the ALT level was 317 U/L. The event of increased ALT resolved on 10 Jan 2002. Laboratory tests on 05 Feb 2002 revealed that the ALT had decreased to 48 U/L. Study medication was discontinued five days after the event occurred on 07 Jan 2002. The patient restarted metreleptin treatment on 09 Feb 2002 at the same starting dose of 0.3 mg BID, which was subsequently titrated to 0.55 mg BID on 02 Apr 2002. Liver enzymes remained stable upon reinitiation of metreleptin with ALT of 48 U/L and AST of 30 U/L on 08 Apr 2002. Of note, the patient also experienced adverse events of influenza and upper respiratory tract infection on 02 Jan and 04 Jan 2000, respectively. The investigator's opinion was that the event of elevated ALT was likely related to the patient's underlying illness of autoimmune hepatitis.

Reviewer comment: This serious adverse event is included as an event of interest, due to the possibility of an exacerbation of the patient's autoimmune disease (autoimmune hepatitis). It is noted that the patient was able to restart metreleptin therapy and transaminases remained stable.

- Hepatic encephalopathy (Patient 90158, NIH Trial); see the description of this serious adverse event in Section 7.3.1, Deaths.

- Still's disease exacerbation: At study entry Patient 648015 (FHA101 Trial) was a 62-year-old white female with an approximate two year history of lipodystrophy (FPL). Relevant medical history included Still's disease, type 2 diabetes, atrial fibrillation, cerebrovascular accident, acute renal failure, hypertension, cholecystectomy, and lung cancer with removal of the center right lobe. Approximately 660 days after initiating metreleptin treatment, the patient presented with pleuritic chest pain. Chest x-ray and CT of the chest were negative for dissection and pulmonary arterial thromboembolism. An echocardiogram showed a small pericardial effusion and normal left ventricular function. Cardiac enzymes were negative. ESR was 34 and C-reactive protein was 4.0 (units not provided). Rhematology was consulted and diagnosed the patient's pain as related to her Still's disease. She was discharged on anakinra and celecoxib. Metreleptin was stopped for three days during the hospitalization. The event did not reappear after reintroduction of metreleptin. The patent continued participation in the trial.

[§§§§§§§] A subsequent serious adverse event also noted that she had a medical history of immunoglobulin A deficiency causing frequent upper respiratory infections, and asthma.

Reviewer comment: This is an event of interest because leptin might exacerbate autoimmune diseases. It is noted that the event did not reappear after metreleptin was restarted.

- Suicide attempt: At study entry, Patient 90136 (NIH Trial) was a 23-year-old Asian female patient with FPL. Relevant past medical history at study entry included past suicide attempts as a teenager, depression, diabetes, and hypertriglyceridemia. At the patient's annual visit to the NIH clinical study site in July 2011 (approximately year 5), the patient told the NIH physician that she was admitted to a psychiatric hospital in (b) (6) (approximately year 4) for an attempted suicide by drug overdose. The patient was hospitalized for six weeks. During the hospitalization, her citalopram was increased to 80 mg, and her anxiety was greatly decreased with the increased citalopram dose. Remeron was administered during the hospitalization and she was discharged on Seroquel 50 mg PRN for panic attacks. The patient stated the reason for attempted suicide was because she 'struggled with what her illness allows her to do in life and struggles with depression and low self-esteem'. The patient was discharged from the hospital on an unspecified date in (b) (6) r (b) (6) and the event of attempted suicide was considered resolved in September 2010. It is unknown if the patient missed metreleptin study medication during the hospitalization. Since being discharged from the psychiatric hospital, the patient denied feeling suicidal and her depressive symptoms as well as anxiety and panic symptoms were well-controlled with medication. The patient reported meeting with a psychiatrist for talk therapy and medication adjustment every two weeks. The investigator stated that during a Jul 2011 NIH clinical study site visit with a social worker, the patient was noted to be psychiatrically stable. Study medication was ongoing and the patient continued participation in the study as of the data collection cutoff date of 11 Jul 2011.

- Suicidal ideation: At study entry, Patient 677002 (FHA101 Trial) was a 25-year-old white female with CGL. Relevant medical history included a prior suicide attempt (unknown date) with no regular psychiatric follow-up in years, diabetes mellitus, gastroparesis, diabetic neuropathy, recurrent nausea and vomiting, and history of food bezoar on endoscopy (Apr 2010). Other medical history included compensated cirrhosis (since 14 years of age; on transplant list since 2001), hypertriglyceridemia, polycystic ovary, retinopathy, microalbuminuria, hypertension, insulin resistance, cholecystectomy, tobacco user (less than one pack per day), and depression. On (b) (6), approximately 195 days after starting metreleptin treatment, the patient experienced suicidal ideation. The patient's mother reported the patient had had suicidal ideation for the past two weeks and had been taken to the emergency room (b) (6) and was given Xanax and discharged without being admitted. The event was considered resolved on 07 Dec 2011. It is unknown if any doses of study medication were missed due to this event. The patient was withdrawn from the study on 07 Dec 2011 by investigator decision (due to family conflict, personal issues, missed appointments, and non-compliance at times).

- Pre-term delivery of non-viable fetus: At study entry, Patient 90156 (NIH Trial) was a 22-year-old Hispanic female with CGL. Relevant medical history included type 2 diabetes, insulin resistance, hypertriglyceridemia, pancreatitis, Hashimoto's thyroiditis, and vitamin D deficiency. The patient experienced a serious adverse event of papillary thyroid cancer in April 2011 for which she underwent thyroidectomy, followed by radioiodine treatment in January 2012 (see narrative in Section 7.6.1, Human Carcinogenicity). This was a retrospectively reported pregnancy case. Information regarding the date of the last menstrual period was not provided. The patient received study drug from conception (approximately (b) (6) (b) (6) based on gestational age) until week 20 of gestation. On (b) (6), after 3.5 years of treatment with metreleptin, the patient was hospitalized due to several days of abdominal pressure during pregnancy. On examination, she had bulging membranes, cervical effacement, and was 1.5 cm dilated. Ultrasound showed approximately 2 cm cervical dilation. The patient was kept on bed rest but continued to dilate. She was given a choice of rescue cerclage, expectant management, or induction termination. She chose cerclage, however, on (b) (6), prior to the procedure, she had membrane rupture. On ultrasound, the fetal legs and part of the abdomen were found to be prolapsing through the cervix. The patient was transferred to labor and delivery, given misoprostol, and delivered the infant via spontaneous vaginal delivery. The infant (female) was born alive and apparently normal for a gestational age of 20 weeks and four days. Birth weight and length were not provided. No resuscitation was attempted, and the expected neonatal demise ensued. The patient's post-delivery course was uncomplicated. She remained afebrile, with no lymphocytosis, and her urinalysis, tests for gonorrhea and Chlamydia, and wet mount were negative throughout hospitalization. Based on clinical examination, she was treated for bacterial vaginosis with metronidazole. She was discharged on (b) (6) and the event of premature delivery was reported resolved. Metreleptin treatment was ongoing and the patient continued participation in the study as of the data cutoff date of 11 Jan 2013.

- Worsening of advanced liver disease (two events): At study entry, Patient 90164 (NIH Trial) was a 16-year-old female of unspecified race with a history of CGL. Relevant medical history included hypertension, cardiomyopathy with pulmonary stenosis, moderate concentric left ventricular hypertrophy with diastolic dysfunction, gastritis, grade III esophageal varices, diabetes with extreme insulin resistance, hyperlipidemia, hypertriglyceridemia, hepatic steatosis with cirrhosis, portal hypertension, hepatic encephalopathy, proteinuria, IgA nephropathy, iron deficiency anemia, and developmental delay. On (b) (6), after approximately 2.2 years of treatment with metreleptin, the patient presented to the emergency room with slightly altered mental status, mild diffuse pruritic rash, and a three month history of increasing abdominal pain and distension. She was hospitalized and reported to have hepatic encephalopathy with an elevated ammonia of 146, lipase 38, lactate 1.6, AST 71, and ALT 63 (units, reference ranges and date obtained not provided).

This was felt by her local physicians to be temporally related to the patient's metformin therapy. Metformin was discontinued and the patient's condition improved. Metreleptin was not interrupted. A CT scan of the abdomen and pelvis on an unspecified date was compared to a prior CT of December 2009 and showed persistent and slightly progressive hepatosplenomegaly (consistent with cirrhosis and portal hypertension); unchanged kidney enlargement; gallbladder swelling without gallstones; and prominent bladder distention. The patient's pain improved after placement of a Foley catheter and administration of lactulose. She was discharged on (b) (6) and the event, reported as worsening of advanced liver disease, was considered resolved. The patient continued trial participation. On (b) (6) (b) (6), the patient again was admitted to the hospital with decreased responsiveness, abdominal pain, and fever. A chest x-ray obtained on admission revealed possible pneumonia. A CT scan of the abdomen (date not specified) showed little change from her previous scan. She was reported to have elevated serum ammonia levels and a negative urinalysis. She was treated with levofloxacin and her condition improved. She was discharged on (b) (6) with discharge diagnoses including hepatic encephalopathy, abdominal pain, pneumonia, and fever. The event, reported as worsening of advanced liver disease, was considered resolved on that date. Study medication was ongoing and the patient continued trial participation as of the data cutoff date of 11 Jan 2013.

Patients Treated for Obesity

The following table enumerates the serious adverse events from the five Amgen trials included in the ISS. In this table, all doses of metreleptin are merged. The ITT Population consists of all patients who received at least one dose of randomized study medication (metreleptin or placebo) during the trial. For trial LEPT-970213, in which eligible patients were randomized into a 24-week treatment period after a four-week metreleptin (10 mg twice daily) induction period, all 228 patients who received at least one dose of metreleptin during the metreleptin induction period are counted as metreleptin-treated patients in the table. Among these 228 patients, 189 patients were randomized to treatment (126:63 metreleptin:placebo) and underwent a 24-week treatment period; those 63 patients randomized to placebo are counted as both metreleptin-treated and placebo-treated, and the analysis were conducted as appropriate depending on the period when data were collected.

Table 47. Incidence of Serious Adverse Events, Population: Obesity ISS Intent-to-Treat (N = 1072)

	Placebo N=351 n (%)	Metreleptin N=784 n (%)
All Serious Adverse Events	13 (3.7)	16 (2.0)
Cardiac disorders	0	4 (0.5)
Angina pectoris	0	2 (0.3)
Atrial fibrillation	0	1 (0.1)
Ventricular arrhythmia	0	1 (0.1)
Gastrointestinal disorders	2 (0.6)	1 (0.1)
Abdominal pain upper	1 (0.3)	1 (0.1)
Pancreatitis	0	1 (0.1)
Diverticulum intestinal	1 (0.3)	0
Rectal hemorrhage	1 (0.3)	0
General disorders and administration site conditions	4 (1.1)	1 (0.1)
Injection site erythema	0	1 (0.1)
Chest pain	2 (0.6)	0
Pyrexia	1 (0.3)	0
Vessel puncture site reaction	1 (0.3)	0
Hepatobiliary disorders	1 (0.3)	0
Cholelithiasis	1 (0.3)	0
Jaundice	1 (0.3)	0
Infections and infestations	3 (0.9)	4 (0.5)
Chronic sinusitis	0	1 (0.1)
Pneumonia	1 (0.3)	1 (0.1)
Sinusitis	0	1 (0.1)
Upper respiratory tract infection	0	1 (0.1)
Injection site abscess	1 (0.3)	0
Meningitis meningococcal	1 (0.3)	0
Injury, poisoning and procedural complications	1 (0.3)	2 (0.3)
Arthropod bite	0	1 (0.1)
Tendon rupture	0	1 (0.1)
Road traffic accident	1 (0.3)	0
Investigations	2 (0.6)	1 (0.1)
Heart rate irregular	1 (0.3)	1 (0.1)
Blood pressure increased	1 (0.3)	0
Metabolism and nutrition disorders	1 (0.3)	0
Hyperglycemia	1 (0.3)	0
Musculoskeletal and connective tissue disorders	0	1 (0.1)

	Placebo N=351 n (%)	Metreleptin N=784 n (%)
Pain in extremity	0	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6)	3 (0.4)
Lymphocytic leukemia	0	1 (0.1)
Metastatic malignant melanoma	0	1 (0.1)
Uterine leiomyoma	0	1 (0.1)
Breast cancer stage III	1 (0.3)*	0
Cervix carcinoma	1 (0.3)*	0
Nervous system disorders	0	3 (0.4)
Cerebrovascular accident	0	1 (0.1)
Cubital tunnel syndrome	0	1 (0.1)
Headache	0	1 (0.1)
Renal and urinary disorders	0	1 (0.1)
Stress urinary incontinence	0	1 (0.1)
Reproductive system and breast disorders	1 (0.3)	0
Ovarian cyst	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)
Asthma	0	1 (0.1)
Surgical and medical procedures	1 (0.3)	0
Cholecystectomy	1 (0.3)	0
*Note: these events occurred in study 980236 (notably not during the randomized portion of study 970213, in which all patients received metreleptin during a run-in period; therefore, neither of these patients were exposed to metreleptin).		

Source: ISS Supporting Data Summary 5.3; version 22 Oct 2010

The narrative for the metreleptin-treated patient with the serious adverse event of pancreatitis is below:

- Patient 17022 (Amgen trial LEPT-970171) was an obese 44-year-old black female with type 2 diabetes treated with glyburide who reportedly had TG values prior to receiving randomized study medication (metreleptin 10 mg BID) ranging from 261 mg/dL to 480 mg/dL. On approximately study day 85, the patient reported stomach cramps. Ten days later, her blood glucose was 165 mg/dL and triglycerides 822 mg/dL. The stomach cramps worsened and the patient was hospitalized three days later. The patient was diagnosed with pancreatitis and treated with intravenous dextrose, sodium chloride, morphine, insulin, and metamucil. She was discharged from the hospital five days later.

The narrative for the metreleptin-treated patient with the serious adverse event of malignant melanoma is below (the other notable malignancy serious adverse event, lymphocytic leukemia, is described above in section 7.3.1, Deaths):

- Patient 15020 (Amgen trial 970171) was a 68-year-old male with type 2 diabetes and hyperlipidemia prior to receiving randomized study medication (metreleptin 10 mg BID). The patient had a history of oral carcinoma five years prior and chest melanoma one year prior, both surgically treated. On study day 101, it was noted that the patient had a firm axillary lymph node. The patient completed the study and the last dose of study drug was study day 112. A biopsy performed 34 days later revealed malignant melanoma. No further information was provided.

Reviewer comment: In addition, note that there were two cancer serious adverse events in placebo-treated patients: events of breast and cervical cancer.

The narrative for the metreleptin-treated patient with serious adverse events of cerebrovascular accident and ventricular arrhythmia is below:

- Patient 13036 (Amgen trial 970171) was a 51-year-old male with type 2 diabetes, obesity, and history of unstable blood pressure prior to receiving randomized study medication (metreleptin 20 mg). On study day 112, he complained of lightheadedness; his blood pressure was 140/98 and heart rate was 96. A mild occipital stroke was diagnosed, he was hospitalized, and study drug was discontinued. The following day, while hospitalized, he developed ventricular tachycardia, which prolonged hospitalization. The tachycardia resolved before discharge two days later.

The following table lists the serious adverse events in patients randomized in the Amgen trials not included in the ISS as well as the Amylin metreleptin + pramlintide for obesity clinical program.

Table 48. Treatment Emergent Serious Adverse Events for Patients Receiving Metreleptin from the Amgen Metreleptin Obesity Program and the Metreleptin + Pramlintide Obesity Program

Preferred Term	Metreleptin	Placebo
	n (%)	n (%)
Amgen LEPT-960176 (N=151)	**n=151**	**N/A**
Breast Neoplasm Malignant	1(0.7)	N/A
Urinary Incontinence	1 (0.7)	N/A
Amgen LEPT-960240 (N=30)	**n=23**	**n=7**
Somnolence	1 (4.3)	0
Amgen LEPT-970211 (N=6)	**n=5**	**n=1**
Asthenia	1 (20.0)	0 (0.0)
Fever	1 (20.0)	0 (0.0)
Headache	1 (20.0)	0 (0.0)
Meningitis	1 (20.0)	0 (0.0)
Vertigo	1 (20.0)	0 (0.0)
Thinking Abnormal	1 (20.0)	0 (0.0)
AMGEN LEPT-950272 (N=250)	**n=177**	**n=73**
Dyspnea	1 (0.6)	0 (0.0)
Fatigue	1 (0.6)	0 (0.0)
Nausea	1 (0.6)	0 (0.0)
Palpitation	1 (0.6)	0 (0.0)
Amgen LEPT-970161 (N=4)	**n=4**	**N/A**
Gastroenteritis Viral	1 (25.0)	N/A
DFA101 (N=83)	**n=83**	**N/A**
Myocardial Infarction	1 (1.2)	N/A
Hypersensitivity	1 (1.2)	N/A
Deep Vein Thrombosis	1 (1.2)	N/A
DFA102 (N=531)	**n=456**	**n=75**
Lymphadenopathy	1 (0.2)	0 (0.0)
Cardiac Arrest	1 (0.2)	0 (0.0)
Goitre	1 (0.2)	0 (0.0)
Non-Cardiac Chest Pain	0 (0.0)	1 (1.3)
Food Allergy	0 (0.0)	1 (1.3)
Papillary Thyroid Cancer	1 (0.2)	0 (0.0)
Parathyroid Tumor Benign	1 (0.2)	0 (0.0)
Cervicobrachial Syndrome	0 (0.0)	1 (1.3)
Convulsion	1 (0.2)	0 (0.0)
Syncope Vasovagal	1 (0.2)	0 (0.0)
Hypertension	0 (0.0)	1 (1.3)
DFA102E (N=273)	**n=242**	**n=31**
Staphylococcal Infection	1 (0.4)	0 (0.0)
Muscle Strain	1 (0.4)	0 (0.0)
Cardiac Enzymes Increased	1 (0.4)	0 (0.0)
Papillary Thyroid Cancer	1 (0.4)	0 (0.0)
DFA103 (N=78)	**n=78**	**N/A**
Breast cancer	1 (1.3)	N/A
DFA104 (N=72)	**n=36**	**n=36**
Coronary Artery Disease	1 (2.8)	0 (0.0)

Note: No serious adverse events were reported for Amgen Studies LEPT-970121, LEPT-970161, LEPT-980219, LEPT-980225, LEPT-980145, and LEPT-980298.

n = number of subjects who experienced the adverse event.

Source: 2013-05-24-bms986109-response-fda-metreleptin-clinical-q1, Attachment 1-Table 1.

Serious adverse events of cancer (breast cancer, Amgen trial LEPT-960176, Patient 01002; papillary thyroid carcinoma, Amylin trial DFA102, Patient 135036; and papillary thyroid carcinoma, Amylin trial DFA102E, Patient 137027) are described in Section 7.6.1, Human Carcinogenicity. Additional serious adverse events of interest are described briefly below:

- Cardiac Arrest and Convulsion (Amylin Trial DFA102; Patient 103011): This patient was a 47-year-old obese white female with a history of vasovagal syncope, vasovagal response secondary to stress, seizures, and blackout episodes since childhood. On Day 60 of metreleptin treatment, the patient was found seizing in her bathroom and was taken to the emergency department where the patient experienced bradycardia and a subsequent nine second episode of asystole. CPR regained a cardiac rhythm. A 10 second syncopal episode followed, resulting in a seizure. The patient was transferred to the intensive care unit for IV fluids and diagnostic testing. Computed tomography, magnetic resonance imagining, chest and spinal x-rays were normal. An electrophysiological study was performed followed by pacemaker insertion. An electroencephalogram revealed a small sharp spike in the right temporal region of questionable clinical significance, but an epliletiform process could not be ruled out.

- Allergic Reaction (Hypersensitivity) (Amylin Trial DFA101; Patient 40431): This patient was a 33-year old obese Asian female with an unremarkable medical history at study entry. On Day 29 of metreleptin therapy, the patient experienced a moderate reaction consisting of itching and hives. Diphenhydramine was administered, the event resolved and study medication was continued. On Day 56 of metreleptin therapy, the patient experienced a reaction consisting of swollen face, hives, and difficulty breathing and concentrating. The patient was seen at an emergency room and admitted overnight for observation with discharge the next day. Study medication was discontinued.

- Meningitis (Amgen Trial LEPT-970211; Patient 1107): This was a 52-year-old male who enrolled in the metreleptin intrathecal trial. A Port-A-Cath was implanted on 20 Nov 1998 and was shown to be situated in the epidural space seven days after implant. The catheter and port were replaced after 14 days and study medication began to be administered 13 days after replacement. On 29 Jan 1999, 44 days after starting study medication, the catheter was dislodged and was replaced, together with the port; study drug was administered successfully on 01 Feb 1999 and 04 Feb 1999. On 05 Feb 1999 the patient complained of "feeling moisture" on his lower back and felt that the catheter was falling out. Meningitis was confirmed with CSF culture and IV cefotaxime initiated. Three days later, the patient was still experiencing headache and fever and was withdrawn from the trial. The investigator attributed the infection to the device.

7.3.3 Dropouts and/or Discontinuations

Patients Treated for Lipodystrophy

In the NIH trials, the most common reason for withdrawal was "other" for eight (11.1%) patients: one due to "stress"[********], one due to "health issues"[††††††††], and six transferred to Named Patient Programs (compassionate use programs) in their respective countries. Four patients (5.6%) discontinued due to "noncompliance". Two patients withdrew because they were deemed ineligible to continue participation in the trial, including one patient (90115) due to a diagnosis of peripheral T-cell lymphoma and one patient (90126) due to the investigator's assessment that the patient was no longer appropriate to continue in the study due to the need to undergo other treatment for an adverse event (i.e., deep vein thrombosis). A total of five patients withdrew due to "adverse events", including deaths. Two patients (90147 and 90114) were withdrawn due to an adverse event (peripheral T-cell lymphoma and proteinuria[‡‡‡‡‡‡‡‡], respectively; the narrative for Patient 90147 is provided in Section 7.6.1, Human Carcinogenicity and the narrative for Patient 90114 is provided below). Three patients experienced serious adverse events that led to death (see Section 7.3.1, Deaths): Patient 90125, pancreatitis with a ruptured pseudocyst, leading to septic shock and subsequent cardiac arrest; Patient 90106, renal failure and subsequent cardiac arrest; and Patient 90158, chronic hepatic failure. One additional withdrawal due to death [anoxic encephalopathy, Patient 90151 (see Section 7.3.1, Deaths)] was reported in the four-month safety update.

Reviewer comment: Although only five patients were considered withdrawal due to adverse events, "stress" in Patient 90105, "health issues" in Patient 90109, peripheral T-cell lymphoma in Patient 90115 and deep vein thrombosis in Patient 90126, could be considered withdrawals due to adverse events as well.

[********] The comments available for this patient's disposition are as follows: *Pt. having psychiatric difficulties – stress at home and living situation which was affecting her ability to comply to any medical regimen or advice*

[††††††††] Patient 90109 was a 13-year old female at study entry with AGL. The patient was withdrawn from the study by the PI approximately 15 months after initiating the trial due to health issues (further details not provided, but medical history for this patient included steatohepatitis, hepatic fibrosis, pancreatitis, proteinuria, and severe hypertriglyceridemia with baseline TG 2984 mg/dL). It is noted that she had the following serious adverse events during the trial that were described in Section 7.3.2, Serious Adverse Events: pancreatitis, hypoalbuminemia, worsening of proteinuria, and worsening of liver disease.

[‡‡‡‡‡‡‡‡] Although five of 72 patients were reported to have withdrawn due to treatment-emergent adverse events in the Clinical Safety Update, during data review for the four-month safety update data cut (11 Jan 2013), it was discovered that Patient 90114 had not withdrawn from the NIH trial but had transferred to a Named Patient Program (non-US, compassionate-use) in July 2009. This patient was erroneously reported as having been withdrawn from the trial due to proteinuria. Nevertheless, the adverse event described a rapid progression of renal disease and the narrative is provided here for completeness. Follow-up on this patient in the Named Patient Program was not provided.

- Proteinuria: At trial entry, Patient 90114 was a 35-year-old male from Madagascar with a 32-year history of AGL. Other relevant past medical history at trial entry included chronic renal failure, proteinuria, hematomegaly, pancreatitis, steatohepatitis, fatigue, hypertriglyceridemia, and type 2 diabetes. At baseline (May 2002), the patient had a serum creatinine of 1.0 mg/dL, with a 24-hr urine protein excretion rate of 2450 mg per 24 hrs. Follow-up tests at the Month 4 visit (23 Sep 2002) showed a serum creatinine of 1.6 mg/dL and 24-hr urine protein excretion rate of 4100 mg per 24 hrs, and at the Month 8 visit (Feb 2003) a serum creatinine of 2.2 mg/dL and 24-hr urine protein excretion rate of 8845 mg per 24 hrs. On 07 Feb 2003, Day 271 of treatment with metreleptin, the patient was withdrawn because of the worsening proteinuria. The event was not considered a serious adverse event. The patient started dialysis nine months after he stopped metreleptin treatment.

Reviewer comment: This appears to be a very rapid progression of MPGN to end stage renal disease. This case is similar to Patient 90109, also with AGL, who developed worsening renal disease (MPGN) on metreleptin. Both cases are described in a 2004 NIH paper, which noted that the contribution of metreleptin cannot be excluded.[30]

In the FHA101 trial, as of the 07 March 2012 data cutoff, 20 of 28 patients were still actively participating. The most common reasons for withdrawal were withdrawal of consent and adverse event (three [11%] patients each). Reasons for withdrawal of consent were desire to get pregnant (Patient 648004), reason unspecified (Patient 648007), and travel burden coupled with lack of efficacy (Patient 648013). Of the three withdrawals due to adverse events, two had a fatal outcome. Patient 648008 experienced a serious adverse event, “loss of consciousness”, which had a fatal outcome (acute bilateral subdural hematomas after a fall). Patient 649001 experienced a serious adverse event of adenocarcinoma, which was a known condition prior to starting metreleptin and which had a fatal outcome. See Section 7.3.1, Deaths, for narratives of both of these events. Patient 648021 was withdrawn due to a non-serious event of muscle spasms, which was assessed by the investigator as related to treatment. In the four-month safety update, no additional patient from trial FHA101 withdrew due to an adverse event.

Patients Treated for Obesity

Withdrawals due to adverse events in the five integrated Amgen trials (ISS) occurred in 79 (10.1%) of 784 metreleptin-treated patients and 20 (5.7%) of 351 placebo-treated patients. The majority of withdrawals due to adverse events in patients treated with metreleptin were due to injection site reactions [38 (4.8%) versus one (0.3%) for placebo] and inflammatory injection-site adverse events including the preferred terms “injection site inflammation”, “injection site pruritus”, “injection site erythema”, and “injection site urticarial” [combined incidence 11 (1.4%) versus 0 (0.0%) for placebo].

Table 49. Incidence of Treatment-Emergent Adverse Events Leading to Withdrawal Summarized by System Organ Class and Preferred Term (Including Preferred Terms with Metreleptin Incidence Greater than Placebo)

System Organ Class Preferred Term	Pbo N=351	Metreleptin N=784
All AEs Leading to Withdrawal	20 (5.7)	79 (10.1)
Eye disorders	0	1 (0.1)
Eye swelling	0	1 (0.1)
Gastrointestinal disorders	2 (0.6)	4 (0.5)
Abdominal pain	0	2 (0.3)
Nausea	1 (0.3)	2 (0.3)
Abdominal distension	0	1 (0.1)
Irritable bowel syndrome	0	1 (0.1)
Pancreatitis	0	1 (0.1)
General disorders and administration site conditions	7 (2.0)	53 (6.8)
Injection site reaction	1 (0.3)	38 (4.8)
Fatigue	0	6 (0.8)
Injection site inflammation	0	4 (0.5)
Injection site pruritus	0	4 (0.5)
Injection site discoloration	0	2 (0.3)
Injection site erythema	0	2 (0.3)
Injection site urticaria	0	2 (0.3)
Chills	0	1 (0.1)
Feeling abnormal	0	1 (0.1)
Injection site vesicles	0	1 (0.1)
Malaise	0	1 (0.1)
Edema	0	1 (0.1)
Swelling	0	1 (0.1)
Infections and infestations	4 (1.1)	5 (0.6)
Hepatitis C	0	1 (0.1)
Influenza	0	1 (0.1)
Lower respiratory tract infection	0	1 (0.1)
Upper respiratory tract infection	0	1 (0.1)
Injury, poisoning and procedural complications	0	1 (0.1)
Arthropod bite	0	1 (0.1)
Metabolism and nutrition disorders	1 (0.3)	2 (0.3)
Decreased appetite	0	1 (0.1)
Musculoskeletal and connective tissue disorders	0	2 (0.3)
Osteoarthritis	0	1 (0.1)
Rotator cuff syndrome	0	1 (0.1)
Neoplasms benign, malignant and unspecified	0	1 (0.1)

Uterine leiomyoma	0	1 (0.1)
Nervous system disorders	1 (0.3)	3 (0.4)
Balance disorder	0	1 (0.1)
Dizziness	0	1 (0.1)
Dysgeusia	0	1 (0.1)
Pregnancy, puerperium and perinatal conditions	0	1 (0.1)
Pregnancy	0	1 (0.1)
Psychiatric disorders	0	2 (0.3)
Depression	0	2 (0.3)
Reproductive system and breast disorders	1 (0.3)	1 (0.1)
Menopausal symptoms	0	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.3)	12 (1.5)
Urticaria	1 (0.3)	8 (1.0)
Rash	0	2 (0.3)
Angioedema	0	1 (0.1)
Circumoral edema	0	1 (0.1)
Psoriasis	0	1 (0.1)

Source: ISS Supporting Data Summary 5.4; version 22 Oct 2010

The table below presents the number of patients with adverse events leading to withdrawal for the Amgen trials not included in the ISS and the Amylin metreleptin + pramlintide for obesity clinical program. Narratives for two events are provided above: (1) meningitis reported in Amgen trial LEPT-970211 and (2) hypersensitivity in Amylin trial DFA101, and one case of papillary thyroid cancer in DFA102 is discussed in Section 7.6.1, Human Carcinogenicity.

In addition, there were several reports related to injection site reactions in the Amgen LEPT-950272 trial that appear to represent both local trauma related to the injection (bruising, erythema, and pain) and also events suggestive of a possible immune reaction (urticaria, pruritis, and rash). There were also two reports of “drug hypersensitivity”, six reports of “hypersensitivity”, and one report of angioedema.

Table 50. Treatment Emergent Adverse Events Leading to Withdrawal from the Amgen Metreleptin Obesity Program and the Metreleptin + Pramlintide Obesity Program

Preferred Term	Metreleptin	Placebo
	n (%)	n (%)
AMGEN LEPT-960176 (N=151)	**n=151**	**N/A**
Dyspepsia	1 (0.7)	N/A
Cough	1 (0.7)	N/A
Respiratory Disorder	1 (0.7)	N/A
Flushing	1 (0.7)	N/A
Lesion Skin	1 (0.7)	N/A
AMGEN LEPT-960240 (N=30)	**n=23**	**n=7**
Headache	1 (4.3)	0 (0.0)
Somnolence	1 (4.3)	0 (0.0)
Joint Stiffness	1 (4.3)	0 (0.0)
Micturition Frequency	1 (4.3)	0 (0.0)
AMGEN LEPT-970121 (N=124)	**n=82**	**n=42**
Asthenia	1 (1.0)	0 (0.0)
Edema Peripheral	1 (1.0)	0 (0.0)
Fever	2 (2.0)	0 (0.0)
Rigors	1 (1.0)	0 (0.0)
Nausea	1 (1.0)	0 (0.0)
Pruritus	3 (4.0)	0 (0.0)
Rash	3 (4.0)	0 (0.0)
Rash Erythematous	1 (1.0)	0 (0.0)
Urticaria	1 (1.0)	0 (0.0)
AMGEN LEPT-970211 (N=6)	**n=5**	**n=1**
Fever	1 (20.0)	0 (0.0)
Headache	1 (20.0)	0 (0.0)
Meningitis	1 (20.0)	0 (0.0)
Device Complication	1 (20.0)	0 (0.0)
AMGEN LEPT-950272 (N=250)	**n=177**	**n=73**
Dermatitis Contact	1 (0.6)	0 (0.0)
Diarrhea	1 (0.6)	0 (0.0)
Erythema	1 (0.6)	0 (0.0)
Fever	1 (0.6)	0 (0.0)
Headache	1 (0.6)	0 (0.0)
Injection Site Ecchymosis	1 (0.6)	0 (0.0)
Injection Site Edema	2 (1.1)	0 (0.0)
Injection Site Erythema	9 (5.1)	0 (0.0)
Injection Site Inflammation	7 (4.0)	0 (0.0)
Injection Site Mass	7 (4.0)	0 (0.0)
Injection Site Pain	3 (1.7)	0 (0.0)
Injection Site Pruritis	5 (2.8)	0 (0.0)
Injection Site Rash	1 (0.6)	0 (0.0)
Injection Site Reaction	1 (0.6)	0 (0.0)
Injection Site Urticaria	1 (0.6)	0 (0.0)
Insomnia	1 (0.6)	0 (0.0)
Malaise	1 (0.6)	0 (0.0)
Palpitation	1 (0.6)	0 (0.0)
Paresthesia	1 (0.6)	0 (0.0)
Pruritis	2 (1.1)	0 (0.0)
Urticaria	1 (0.6)	0 (0.0)
Vomiting	1 (0.6)	0 (0.0)

Preferred Term	Metreleptin	Placebo
	n (%)	n (%)
DFA101 (N=83)	**n=83**	**N/A**
Myocardial Infarction	1 (1.2)	N/A
Nausea	1 (1.2)	N/A
Injection Site Pruritus	1 (1.2)	N/A
Injection Site Scar	1 (1.2)	N/A
Drug Hypersensitivity	1 (1.2)	N/A
Hypersensitivity	3 (3.6)	N/A
DFA102 (N=531)	**n=456**	**n=75**
Abdominal Pain Upper	1 (0.2)	0 (0.0)
Nausea	3 (0.7)	0 (0.0)
Injection Site Erythema	1 (0.2)	0 (0.0)
Injection Site Nodule	1 (0.2)	0 (0.0)
Injection Site Pruritus	1 (0.2)	0 (0.0)
Injection Site Rash	1 (0.2)	0 (0.0)
Injection Site Urticaria	4 (0.9)	0 (0.0)
Drug Hypersensitivity	1 (0.2)	0 (0.0)
Hypersensitivity	2 (0.4)	0 (0.0)
Kidney Infection	1 (0.2)	0 (0.0)
Blood Creatine Phosphokinase Increased	1 (0.2)	2 (2.7)
Blood Pressure Increased	0 (0.0)	1 (1.3)
Papillary Thyroid Cancer	1 (0.2)	0 (0.0)
Menorrhagia	1 (0.2)	0 (0.0)
Angioedema	1 (0.2)	0 (0.0)
Generalised Erythema	1 (0.2)	0 (0.0)
Urticaria	2 (0.4)	0 (0.0)
DFA102E (N=273)	**n=242**	**n=31**
Abdominal Pain	1 (0.4)	0 (0.0)
Injection Site Nodule	1 (0.4)	0 (0.0)
Hypersensitivity	1 (0.4)	0 (0.0)
DFA104 (N=72)	**n=36**	**n=36**
Coronary Artery Disease	1 (2.8)	0 (0.0)

N/A=not applicable
Note: No adverse events leading to withdrawal were reported for Amgen Studies LEPT-970161, LEPT-980219, LEPT-980225, LEPT-980145, LEPT-980298, and DFA103.
For Amgen studies multiple events may have been recorded for a subject as an adverse event leading to withdrawal whereas for the pramlintide+metreleptin studies only the primary event which led to the withdrawal was recorded.

Source: Response to FDA Request for Information Dated 24-May-2013, Attachment 1 Table 2

7.3.4 Significant Adverse Events

I believe that two safety concerns can be considered “significant”: malignancy and immunogenicity.

Leptin, its implication in the development of cancer, and adverse events of malignancies seen in the clinical trials (lipodystrophy and non-lipodystrophy programs) are discussed in Section 7.6.1, Human Carcinogenicity.

The immunogenicity of metreleptin is discussed in Section 7.4.6, Immunogenicity.

7.3.5 Submission Specific Primary Safety Concerns

Hypoglycemia

Hypoglycemia of either mild or moderate intensity was the most frequent adverse event in the lipodystrophy trials, reported in eight (11.1%) of 72 patients (nine events) in the NIH trials and in seven (25.0%) of 28 patients (13 events: 11 mild, one moderate, one severe) in trial FHA101.

In the NIH trials, hypoglycemia was reported only in those patients receiving concomitant insulin therapy (short-acting, long-acting, or Humulin-R, U-500) with or without oral anti-hyperglycemic agents (including sulfonylureas, metformin, and thiazolidinediones). No severe hypoglycemia events (e.g., requiring the assistance of another individual) were reported. Two hypoglycemia events occurred in Patient 90102. The patient's insulin regimen (ultralente and regular insulin) was discontinued after the second event; no events of hypoglycemia were reported for this patient after discontinuation of insulin.

In trial FHA101, one patient (677001) experienced a severe event of hypoglycemia that required assistance from another person and was considered a serious adverse event although the patient was not taken to the hospital (see the narrative in Section 7.3.2, Serious Adverse Events). One patient (648020) had five events of hypoglycemia reported.[§§§§§§§§] Most events of hypoglycemia occurred in patients who were receiving concomitant insulin therapy or a sulfonylurea with or without other oral antihyperglycemic agents, except Patient 648022 who experienced the event of hypoglycemia while on metformin approximately five months after starting metreleptin and had been on levemir and humalog insulins until about 3-4 months before the event. Concomitant diabetes therapy in these patients included rapid-acting, short-acting and long-acting insulins, U-500 insulin and insulin mixtures, as well as oral agents including sulfonylureas, metformin, and gliptins.

At the four-month safety update, 10 (11.1%) of 90 patients in the NIH trial reported hypoglycemia (two new events since the previous data cutoff). The two new events of hypoglycemia in two patients (one "occasional" and the other "intermittent" hypoglycemia) were both ongoing at the time of the four-month safety update data cutoff. These events were considered by the investigator as mild in intensity. Both patients were receiving concomitant insulin at the time of the events.

At the four-month safety update, 12 of 35 (34.3%) patients in the trial FHA101 reported hypoglycemia (including five patients with 12 new events). Seven of these events were considered mild, four moderate and one severe. This severe event was considered by the investigator as serious (see the narrative in Section 7.3.2, Serious Adverse Events;

[§§§§§§§§] This was a 58 yo F with FPL, who at baseline had an HbA1c of 8.1% and FPG of 61 mg/dL.

this occurred in Patient 648005, who had a total of three hypoglycemia adverse events[*********] reported in the four-month safety update). All of the hypoglycemia events occurred in patients who were receiving concomitant insulin therapy or a sulfonylurea with or without other oral antihyperglycemic agents. Concomitant diabetes therapy in these patients included rapid-acting, short-acting and long-acting insulins, U-500 insulin and insulin mixtures, as well as oral agents including sulfonylureas, metformin, and gliptins.

In the five Amgen obesity trials in the ISS, hypoglycemia was reported overall in 3.6% and 1.4% in metreleptin- and placebo-treated patients, respectively. Hypoglycemia was reported only in the two trials in obese patients with type 2 diabetes (LEPT-970171 and LEPT-970188); in these trials the incidence in metreleptin-treated patients was 14.3% and in placebo-treated patients, 5.0%. Patients in LEPT-970171 were on stable doses of either glipizide or glyburide prior to the study, but dose adjustment was permitted during the study to minimize hypoglycemia, [†††††††††] whereas patients in LEPT-970188 had diet-treated diabetes and were prohibited from taking oral hypoglycemic agents within 12 weeks of screening. No hypoglycemia adverse events were reported in obese patients without diabetes.

A total of 11 metreleptin-treated patients reported hypoglycemic events compared to eight placebo-treated patients in the Amgen trials not included in the ISS and the metreleptin + pramlintide for obesity clinical program. All hypoglycemic events occurred in placebo-controlled trials. None of these events was considered serious and none led to study withdrawal. Events occurred with similar incidence in metreleptin- and placebo-treated patients.

Pancreatitis

Patients with lipodystrophy are predisposed to acute pancreatitis, due to marked hypertriglyceridemia (often defined as TG greater than 1000 mg/dL). In the NIH trials, 16 (22.2%) patients had a medical history of pancreatitis and 4 (5.6%) patients had a history of recurrent pancreatitis. Although some patients treated with metreleptin appeared to have significant improvement in TG concentrations, many patients continued to have high or fluctuating TGs, and adverse events of pancreatitis were seen in the lipodystrophy trials. As there was no control group, and the trials were not powered to detect either an improvement or worsening in pancreatitis, it is difficult to know the impact of metreleptin on pancreatitis in a patient population predisposed to this adverse event. The sponsor has proposed that patients who developed pancreatitis were non-compliant or they discontinued or interrupted metreleptin too rapidly with subsequent rebound in serum TG.

[*********] This patient also had a witnessed transient 'loss of consciousness' event reported, although without a blood sugar reported and no further information provided.
[†††††††††] Sulfonylurea use between groups was not described.

Reviewer comment: While it is reasonable to conclude that lack of metabolic control (whether it is due to noncompliance with metreleptin, diet, or concomitant medications) might put a patient with severe hypertriglyceridemia at risk for pancreatitis, I could not confirm a causal association between noncompliance and/or abrupt discontinuation and pancreatitis in all cases. Please see the narratives below.

In the NIH trials, 20 (27.8%) of the 72 patients had a medical history of pancreatitis (16, 22.2%) or recurrent pancreatitis (4, 5.6%), and in FHA101, two (8%) of 25 patients with medical history captured had a history of pancreatitis.

The following table summarizes pancreatitis serious adverse events and non-serious adverse events for the lipodystrophy trials; narratives of pancreatitis serious adverse events follow. Of note, each patient who developed pancreatitis in the trial had a history of pancreatitis.

Table 51. Adverse Events of Pancreatitis in the Lipodystrophy Trials

Patient ID Age / Sex / Type	Relevant Medical History / Baseline TG	Verbatim Term / SAE?	Time to Onset (Days)
90101 17 / F / AGL	Pancreatitis Hypertriglyceridemia TG 7420 mg/dL Xanthoma	Recurrent pancreatitis / N	268
		Pancreatitis / Y	4084
90109 13 / F / AGL	Pancreatitis Hypertriglyceridemia TG 2984 mg/dL Xanthoma	Pancreatitis attack / Y	168
90121 32 / F / FPL	Pancreatitis Hypertriglyceridemia TG 2324 mg/dL Xanthoma Chronic abdominal pain	Acute exacerbation of pancreatitis / Y	43
90125 15 / F / CGL	Pancreatitis TG 1669 mg/dL	Bout of pancreatitis / Y	104
90138 34 / F / FPL	Pancreatitis Hypertriglyceridemia TG 359 mg/dL	Pancreatitis / Y	876
648001 9 / F / AGL	Acute pancreatitis High triglycerides TG 10623 mg/dL	Acute pancreatitis / Y	191
		Pancreatitis / Y	1205

Source: Clinical Safety Update, Table 43; Four-month safety update, Attachment 1

Serious Adverse Events of Pancreatitis

Serious adverse events of pancreatitis are described in more detail here:

- NIH Patient 90101: At study entry (02 Aug 2000), this was a 17-year-old white female with a history of AGL. Other relevant medical history included hypertriglyceridemia, insulin resistance, recurrent pancreatitis, diabetes mellitus, diabetic nephropathy, hepatomegaly, abdominal pain, nausea, vomiting, inflamed [redacted]l, asthma, scoliosis, kidney enlargement, and hepatic steatosis. On [redacted] after 11 years of treatment, the patient was taken to the emergency room for nausea, vomiting, and abdominal pain, and was admitted the following morning. Laboratory tests showed a lipase greater than 5000, TG 300, and blood glucose values of 350 and 237 (units and reference ranges not specified). She was diagnosed with pancreatitis and treated with bowel rest, nasogastric drainage, intravenous fluids, hydromorphone, and SC insulin. She was also felt to have an ileus. The patient was not sure what triggered the pancreatitis as "her triglycerides had been good lately," and she did not alter her diet; she thought that it may have been related to vomiting associated with her recent menstrual period. There was no indication of non-compliance in terms of the pancreatitis event. An upper gastrointestinal study (unspecified) was performed on [redacted] (results not available); superior mesenteric artery syndrome was diagnosed and thought to be the cause of some of the patient's symptoms. The patient underwent duodenojejunostomy on [redacted] and recovered uneventfully. The superior mesenteric artery syndrome and pancreatitis were reported resolved on 17 Oct 2011. Metreleptin treatment was continued through the hospital course and the patient continued participation in the study as of the data cutoff date of 11 Jan 2013.

- NIH Patient 90109: At study entry [redacted] this was a 13-year-old white female with a seven-year history of AGL. Other relevant past medical history at study entry included episodes of pancreatitis (most recent episode Jun 2001) and hypertriglyceridemia (6000-10000 mg/dL prior to metreleptin therapy and 3000-6000 mg/dL after starting metreleptin therapy). At baseline, the patient's TG was 2984 mg/dL with subsequent values after starting metreleptin treatment of 6910 mg/dL on 17 Oct 2001, 2842 mg/dL on 26 Nov 2001, and 5795 mg/dL on 28 Jan 2002. On [redacted], Day 169 of treatment with metreleptin, the patient experienced the sudden onset of abdominal pain, nausea, and vomiting. The amylase concentration was 377 U/L (normal range: 25-125 U/L), and a presumptive diagnosis of pancreatitis was made. The patient was admitted for NPO status and IV fluid therapy, and was discharged on [redacted]. The event of pancreatitis was considered resolved after approximately one month on 28 Mar 2002. The patient continued participation in the study and receiving metreleptin treatment until she experienced a serious adverse event of hypoalbuminemia, proteinuria, and worsening liver disorder, after which she was withdrawn from the trial. She died approximately nine months later (see description in Section 7.3.1, Deaths).

Reviewer comment: Note that despite the report of TG values 6000-10,000 mg/dL prior to starting metreleptin, the patient's baseline TG value was recorded as 2984 mg/dL (suggesting that TG concentrations in some patients are very variable, and may be influenced by a number of factors, including diet). She continued to have very high TG values after metreleptin therapy, even during times of reported compliance with metreleptin therapy.

- NIH Patient 90121: At study entry (b) (6) this was a 32-year-old white female with FPL. Other relevant past medical history at study entry included history of multiple episodes of pancreatitis (further details not available), chronic abdominal pain, hypercholesterolemia, hypertriglyceridemia, steatohepatitis, and diabetes. At baseline, TG was 2324 mg/dL. On (b) (6), Day 44 of treatment with metreleptin, the patient was hospitalized with pancreatitis. Further details regarding this event of pancreatitis are not available. The event of pancreatitis resolved after 47 days on 01 May 2003. TG at the Month 4 visit (11 Jun 2003) was 530 mg/dL. The decision was made on 31 Aug 2004 to withdraw the patient from the trial as the investigator questioned her compliance with taking study medication. Metreleptin was tapered over the next week, and the patient took her last dose of study medication on 31 Aug 2004.

Reviewer comment: Of note, the patient's Month 8 TG was 752 mg/dL and the Month 12 TG was 1825 mg/dL. According to the information available, fenofibrate and omega-3 fatty acids were started at or before the Month 4 visit.

- NIH Patient 90125: This pancreatitis event was discussed above in Section 7.3.1, Deaths.

Reviewer comment: Patient compliance was questioned in this case; however, it is unknown whether the pancreatitis even can be ascribed to the patient's TGs being high because she was not taking metreleptin, or whether the drug was stopped without a taper and her TGs rapidly increased (as proposed by the investigator). Her baseline TG value was 1669 mg/dL, but there are not any additional follow-up values available.

- NIH Patient 90138: At study entry (b) (6)), this was a 34-year-old female with FPL. Relevant medical history at study entry included pancreatitis. The patient presented with cold/flu-like symptoms for several days with nausea, vomiting, and diarrhea. On (b) (6), Day 870 of metreleptin treatment, she was hospitalized with a presumptive diagnosis of colitis. The hospital physician stopped metreleptin therapy on (b) (6) without consulting the study investigators. On (b) (6) (b) (6) it was noted that amylase and lipase levels had dramatically risen (values unavailable) from baseline at time of hospitalization on (b) (6). The patient subsequently developed pancreatitis. Further details about the pancreatitis are not

available. Metreleptin therapy was restarted on (b) (6) and the patient was discharged from the hospital on (b) (6). The events of colitis and pancreatitis resolved after approximately seven days, and the patient had no further episodes of pancreatitis. The event of pancreatitis was felt by the investigator to have occurred due to the abrupt withdrawal of metreleptin.

Reviewer comment: No details were provided about this hospitalization, so it is difficult to comment on the assertion that pancreatitis was due to abrupt metreleptin withdrawal (i.e., it is not clear if the diagnosis of colitis was in fact early pancreatitis, what other medications may have been stopped at the time of hospitalization, or what the TG values were at the time of diagnosis). The patient's available TG values were as follows: baseline: 359 mg/dL, Month 4: 405 mg/dL, Month 12: 295 mg/dL, Year 2 (last available value prior to hospitalization, (b) (6)): 873 mg/dL, unscheduled visit May 2011 963 mg/dL. Compliance was not recorded for this patient. She was on fenofibrate at baseline, which continued throughout the trial. Fish oil was added to her regimen at or before the Month 4 visit.

- NIH Patient 90180 (enrolled subsequent to the July 2011 data cut; these are adverse events of "abdominal pain", not "pancreatitis"): At study entry (b) (6) (b) (6) this was a 28-year-old white female with FPL. Other relevant medical history included hypertension, chronic pancreatitis (usually in conjunction with hypertriglyceridemia of 500 to 14000 mg/dL), extreme insulin resistance with type 2 diabetes, diabetic ketoacidosis, duodenitis, gastroesophageal reflux disease, constipation, polycystic ovary syndrome, menstrual irregularities, anemia, chronic pain disorder (with chronic opioid use), and prior cholecystectomy. Prior to metreleptin therapy, she reportedly had attacks requiring hospitalization every 3 to 4 weeks. She was admitted to the hospital on (b) (6) (b) (6) with similar symptoms of abdominal pain and nausea. On (b) (6), laboratory tests showed TG of 2300 mg/dL, and normal amylase and lipase (results not provided). A consultant noted that the patient struggled with binge eating disorder. Her diet was advanced and she was able to tolerate a regular diet with some mild abdominal cramps and slight nausea. She was discharged from the hospital on (b) (6), with TG of 405 mg/dL and lipase 73 U/L on the day of discharge. On (b) (6), Day 108 of treatment with metreleptin, the patient was admitted to the hospital with abdominal pain, poorly controlled diabetes, and electrolyte and acid-base disturbances. She stated that she had been feeling more hungry and eating more than usual for approximately two weeks. On (b) (6), she missed her morning dose of metreleptin and did not realize it until taking her evening dose; she also stated that her insulin pump ran out of medication around 4 p.m. She ate dinner, and several hours later began having severe, sharp, epigastric pain, radiating to the back, associated with abdominal bloating and regurgitation of food, but no frank emesis. Upon admission, her amylase and lipase were within normal limits; TG (fasting) one day after being admitted was 8861 mg/dL and

glucose 432 mg/dL. A CT scan of the abdomen and pelvis with contrast revealed a diffuse fatty liver; no evidence of acute pancreatitis; and a collapsing right corpus luteum with a small amount of free pelvic fluid. The patient received ondansetron and promethazine. Metreleptin therapy was continued. Her condition improved and at discharge, TG was 614 mg/dL. On (b) (6) Day 197 of treatment with metreleptin, the patient was hospitalized for abdominal pain and nausea. She had not previously missed any metreleptin doses or eaten any large and/or fatty meals. Fasting laboratory tests showed TG of 5881 mg/dL and lipase 82 U/L. The patient received ondansetron, promethazine, and hydromorphone. Metreleptin therapy was continued. Further details of the patient's hospital course were not available at the time of this report. The event of abdominal pain resolved on 14 Dec 2012. The patient continued participation in the study as of the data cutoff date of 11 Jan 2013.

Reviewer comment: The three adverse events reported for this patient were named "abdominal pain"; however, they occurred in conjunction with elevated TGs in a patient who has a history of similar attacks of low amylase and lipase and high TGs. These cases are of relevance, because in at least one instance, they occurred when the patient was purportedly compliant with her metreleptin treatment.

- FHA101 Patient 648001 (two events): At study entry (b) (6) this was a 9-year-old black female with juvenile dermatomyositis and AGL diagnosed in 2007. Relevant medical history at study entry included history of acute pancreatitis (two episodes: one in 2008 and one in 2009), insulin resistance, type 1 diabetes mellitus, high triglycerides, increased liver size and fatty infiltration of liver, minimal proteinuria, history of nausea and vomiting, and heartburn. At baseline, the patient's TG was 10623 mg/dL. Following metreleptin treatment, the TG decreased to 1059 mg/dL at Month 3 (29 Jun 2009) and increased to 3901 mg/dL at Month 6 (22 Sep 2009). On (b) (6), day 192 of metreleptin treatment, the patient experienced nausea, vomiting, and pain in her flanks and lower abdomen. The patient developed a fever and poor appetite two days later. On admission to the hospital, lipase was 303 IU/L (normal 5-50 IU/L) and amylase was 91 (normal 30-100 U/L). The blood sample was noted to be lipemic but TG was not reported. Results of the CT scan were consistent with pancreatitis. The patient was discharged on (b) (6). Study medication was stopped during hospitalization, but restarted upon discharge. Follow-up TG values were: 2743 mg/dL on 04 Nov 2009, 4594 mg/dL at Month 9, 4296 mg/dL at Month 10, 3566 mg/dL at Month 11, and 140 mg/dL at Month 12. On (b) (6), approximately 3.3 years after initiating metreleptin therapy, she experienced worsening migraine with vomiting and was taken to the emergency room. Her blood glucose was 179 mg/dL prior to going the ER. Upon arrival at the ER, she complained of sharp, diffuse abdominal pain, and was febrile with a temperature of 38.6°C and heart rate 140-150 bpm. Laboratory tests showed a lipase level of 4622 U/L, and a blood glucose of 542, pH 7.21, and anion gap 27. On admission to the pediatric ICU, she was found to be in mild DKA with + urine

ketones, TG 18110 mg/dL, lipase 1710 U/L, amylase 701 IU/, and creatine phosphokinase 428 IU/L (NR 26-180). Her CT scan was interpreted at the hospital as showing pancreatic enlargement. Of note, at her most recent scheduled visit prior to this hospitalization on (b) (6) her TG was 1541 mg/dL. Plasmapheresis was performed, with TG decreasing to 4022 mg/dL and then 3071 mg/dL. She experienced abdominal pain and distention. An abdominal x-ray on (b) (6) was consistent with an ileus. On (b) (6), the patient's amylase was 201 IU/L, lipase 427 U/L, and TG 3169 and 1452 mg/dL. Metreleptin therapy was restarted on (b) (6). On (b) (6), the patient's TG was 602 mg/dL and lipase was 151 U/L. The patient was discharged on (b) (6). The patient continued participation in the study.

Reviewer comment: Compliance with metreleptin was not reported in the narrative, although according to additional information provided by the sponsor, the PI believed there was a compliance issue with metreleptin, insulin, and diet. It is noted that she was started on omega-3 fatty acids in addition to fenofibrate and simvastatin at Month 6.

In addition to pancreatitis events in the lipodystrophy trials, there was one event of pancreatitis on Day 85 in a patient with obesity treated with metreleptin in the Amgen trial LEPT-970171. This case was discussed above in Section, 7.3.2, Serious Adverse Events. No pancreatitis adverse events were reported in the 10 Amgen trials not included in the ISS or the metreleptin + pramlintide for obesity clinical program.

In the compassionate use programs and investigator-initiated trials, five pancreatitis-related serious adverse events were reported, all in patients with lipodystrophy. Four out of the five patients had pre-existing hypertriglyceridemia and one patient had a history of gallstones. Two of the cases were reportedly associated with metreleptin non-compliance.

Table 52. Individual Patient Data for Patients with Pancreatitis-Related Serious Adverse Events: Metreleptin in Compassionate-Use and Investigator-Initiated Trials

Compassionate Use Trials (Named Patient Program)					
Indication	Study ID Age / Sex / Type	Relevant Medical History	SAE	Time to Onset	Relevant Comments
Lipodystrophy	NPP-Germany 24 / F / partial lipodystrophy	Diabetes mellitus, hypertriglyceridemia, pancreatitis (4 events prior to start of metreleptin treatment)	Pancreatitis	480 days	Metreleptin continued at an increased dose to assist with control of pancreatitis
Lipodystrophy	NPP-United Kingdom 55 / F / partial lipodystrophy	Hepatic steatosis, mildly elevated liver enzymes, fatty liver, gallstones, cholecystectomy	Pancreatitis	6 days	The reporting physician requested the event term be updated to abdominal pain cause unknown, possibly mild pancreatitis.
Investigator-Initiated Trials					
Lipodystrophy	20020368 33 / F / not reported	Hypertriglyceridemia, diabetes, bipolar disorder	Pancreatitis acute	Approximately 8 months	Ultrasound showed enlarged fatty liver, normal gallbladder, poorly visualized pancreas. Diagnosed with possible acute pancreatitis.
Lipodystrophy	20020701 (and extension study) 18 / F / CGL	Hypertriglyceridemia, diabetes, treatment non-compliance, Bell's palsy	2 events of pancreatitis	Approximately 15 months and 19 months	Patient was treatment non-compliant, poorly controlled diabetes, HbA1c 11.2%, glucose 352 mg/dL, diabetic kketoacidosis on admission, TG 5250 mg/dL

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-10

Liver-Related Adverse Events

Patients with lipodystrophy who have undergone liver biopsy have been described to fall within the spectrum of non-alcoholic fatty liver disease (NAFLD), from none to inflammation and fibrosis (including cirrhosis), as well as having other liver diseases such as autoimmune hepatitis. Historically, cirrhosis has been reported in about one-fifth of AGL patients as a late sequela of hepatic steatosis or autoimmune hepatitis.[2] In CGL, hepatomegaly from fatty liver is reported to be almost universal and may lead to cirrhosis.[2]

In the NIH trial, 32 (44%) patients had a medical history of steatohepatitis and 14 (19.4%) patients had a history of hepatic steatosis. Six (8.3%) patients had cirrhosis (three of whom also had steatohepatitis), and four (5.6%) patients had hepatic fibrosis (one also with steatohepatitis, two also with autoimmune hepatitis, one also with hepatic steatosis). Six percent of patients with AGL and 16% of patients with CGL had cirrhosis at baseline (cirrhosis was not reported in patients with partial lipodystrophy). In the FHA101 trial, 19 (76%) of 25 patients (with medical history captured) had a medical history of hepatic steatosis, and one (4%) of 25 patients had a medical history of autoimmune hepatitis.

Table 53. Liver-Related Adverse Events in the Lipodystrophy Trials

Patient ID Age / Sex / Type	**Relevant Medical History (Baseline AST / ALT)**	**Verbatim Term / SAE?**	**Time to Onset (Days)**
90103 27 / F / AGL	Autoimmune hepatitis, liver fibrosis (AST 57, ALT 128)	Increased liver enzymes / Y	481
90107 42 / F / FPL	Hepatomegaly, focal glomerulonephritis (AST 28, ALT 28)	Steatohepatitis / N	6
90109 13 / F / AGL	Nonalcoholic steatohepatitis, bridging fibrosis (AST 85, ALT 79)	Chronic inflammatory hepatitis / N	382
		Worsening of liver disease / Y	422
90110 8 / F / AGL	Autoimmune hepatitis, mild portal fibrosis, fatty liver (AST 38-39, ALT 53-56)	Elevated ALT level of 317 U/L / Y	34
		Worsening autoimmune hepatitis / N	2443
90158 18 / F / AGL	Severe liver disease with cirrhosis (AST 142, ALT 105)	Hepatic encephalopathy / Y	344
		Progressive end stage liver disease / Y (fatal)	523
648004 30 / F / FPL	Fatty liver, increased LFTs (AST 21, ALT 14)	Elevated AST levels (AST 78, ALT 33) / N	443

648016 11 / M / AGL	Chronic active autoimmune hepatitis, history of elevated LFTs (AST 208, ALT 419)	Increased LFTs / N	9

Reviewer comment: Note that five out of seven cases occurred in patients with AGL, three of whom had known autoimmune hepatitis at baseline. Patients with AGL and autoimmune hepatitis may be at risk for exacerbation of autoimmune hepatitis with metreleptin.

The following table presents a categorical summary of patients who had increases in AST or ALT at least three, five, or 10 times the upper limit of normal (ULN) at least one time or at two or more consecutive visits. Notably all patients with categorical increases in transaminases had a diagnosis of chronic liver disease at baseline (typically steatohepatitis, cirrhosis, and/or autoimmune hepatitis) except for Patient 90142 who had a history of hepatomegaly and substantially elevated transaminases at baseline but without a specific diagnosis of liver disease. No patient met the criteria for 2X ULN for total bilirubin (therefore, no patient met the criteria for Hy's Law[‡‡‡‡‡‡‡‡‡]). One patient (90158) who had a medical history of severe liver disease with cirrhosis had a slightly elevated total bilirubin measurement at baseline (1.1 mg/dL) which increased to 1.7 mg/dL at Month 8. This patient died due to progressive end stage liver disease. See the narrative in Section 7.3.1, Deaths.

[‡‡‡‡‡‡‡‡‡] "Hy's Law": Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). See: *Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation.*

Table 54. Categorical Summary of AST and ALT Values, NIH Trials

Analyte Category	Generalized Lipodystrophy n (%) [RPY]	Partial Lipodystrophy n (%) [RPY]	All Patients n (%) [RPY]
AST (IU/L)			
N with at least 1 post-BL measurement	**46**	**22**	**68**
Post-BL ≥3 X ULN at least 1 time	9 (19.6) [0.048]	2 (9.1) [0.022]	11 (16.2) [0.040]
Post-BL ≥5 X ULN at least 1 time	6 (13.0) [0.032]	2 (9.1) [0.022]	8 (11.8) [0.029]
Post-BL ≥10 X ULN at least 1 time	2 (4.3) [0.010]	0 (0.0) [0.000]	2 (2.9) [0.007]
N with at least 2 post-BL measurements	**40**	**21**	**61**
Post-BL ≥3 X ULN at 2 or more consecutive visits	2 (5.0) [0.010]	1 (4.8) [0.011]	3 (4.9) [0.011]
Post-BL ≥5 X ULN at 2 or more consecutive visits	1 (2.5) [0.005]	1 (4.8) [0.011]	2 (3.3) [0.007]
Post-BL ≥10 X ULN at 2 or more consecutive visits	1 (2.5) [0.005]	0 (0.0) [0.000]	1 (1.6) [0.004]
ALT (IU/L)			
N with at least 1 post-BL measurement	**46**	**22**	**68**
Post-BL ≥3 X ULN at least 1 time	8 (17.4) [0.045]	5 (22.7) [0.065]	13 (19.1) [0.051]
Post-BL ≥5 X ULN at least 1 time	6 (13.0) [0.032]	2 (9.1) [0.023]	8 (11.8) [0.029]
Post-BL ≥10 X ULN at least 1 time	2 (4.3) [0.010]	1 (4.5) [0.011]	3 (4.4) [0.010]
N with at least 2 post-BL measurements	**40**	**21**	**61**
Post-BL ≥3 X ULN at 2 or more consecutive visits	2 (5.0) [0.010]	3 (14.3) [0.037]	5 (8.2) [0.018]
Post-BL ≥5 X ULN at 2 or more consecutive visits	2 (5.0) [0.010]	2 (9.5) [0.023]	4 (6.6) [0.014]
Post-BL ≥10 X ULN at 2 or more consecutive visits	0 (0.0) [0.000]	0 (0.0) [0.000]	0 (0.0) [0.000]

BL = baseline.

Notes: Increases are from baseline, which is defined as the last available value before the patient received the first injection of metreleptin.
- [RPY] = Rate per Patient Year, derived by dividing n by patient years of exposure. If a patient had the event, their exposure is truncated at the time of event.
- Normal ranges were not collected. For the purposes of this analysis, 34 IU/L was used as the upper limit of normal (ULN) for AST and 41 IU/L was used for ALT.

Source: Clinical Safety Update, Table

In the FHA101 trial, mean values for ALT and AST were slightly above the upper limit of normal for the overall population (N = 28) (ALT [mean ± SE] 54 ± 16 U/L, AST 39 ± 8 U/L). In those patients with elevated baseline values (n = 9 for ALT, n = 7 for AST), ALT decreased from 133 ± 56 to 41 ± 6, and AST from 91 ± 28 U/L to 36 ± 4 U/L at Month 6. These improvements were primarily driven by two patients with AGL: Patient 648016 with ALT decreasing from 419 to 89 U/L and AST from 208 to 36 U/L) at Month 6 (see the liver-related adverse event reported in this patient in the table above), and Patient 648022 with ALT decreasing from 259 to 19 U/L and AST from 145 to 20 U/L at Month 6. No patients in FHA101 had an increase in ALT or AST greater than 3X ULN, nor did any patient have a total bilirubin elevation greater than 2X ULN.

No liver-related adverse events were reported in metreleptin-treated patients across the five integrated obesity trials from the ISS: LEPT-970164, LEPT-970213, LEPT-980236, LEPT-970188, and LEPT-970171. In metreleptin-treated patients, mean changes from baseline to the last post-baseline assessment were -0.7 U/L versus -0.2 U/L for placebo for AST and -2.0 U/L versus -0.7 U/L for placebo for ALT. There was a slightly higher incidence (0.7% vs. 0.3%) for metreleptin-treated patients meeting ALT 3X ULN criteria compared to placebo. No patients (metreleptin or placebo) who met criteria for

increases in AST or ALT greater than 3X ULN had increases in total bilirubin greater than 2X ULN; therefore, there were no cases that met the criteria of Hy's Law.

In the Amgen trials not included in the ISS as well as the metreleptin + pramlintide for obesity clinical program, the following liver-related adverse events were reported (no further details were provided):

- One case of blood bilirubin increased in a metreleptin-treated patient
- Three cases of ALT increased in metreleptin-treated patients and one case in a placebo-treated patient
- Three cases of AST increased in metreleptin-treated patients and one case in a placebo-treated patient

Nephropathy

Lipodystrophy Trials

A high incidence of proteinuric nephropathies [e.g., membranoproliferative glomerulonephritis (MPGN) and focal segmental glomerulosclerosis (FSGS) as well as diabetic nephropathy] has been noted in patients with generalized lipodystrophy.[30] Acquired partial lipodystrophy is also associated with a higher frequency of MPGN.[2]

In the NIH trials, 24 (33%) patients, and in FHA101, seven (28%) patients had a medical history of proteinuria. Four (5.6%) patients in the NIH study had a medical history of glomerular disease (three with FSGS, two of whom also had proteinuria, and one with focal glomerulonephritis, also with proteinuria).

Adverse Events

The table below summarizes adverse events relevant to proteinuric nephropathies. Individual patient narratives for those events that were deemed serious can be found in Section 7.3.1, Deaths (Patient 90106) and Section 7.3.2, Nonfatal Serious Adverse Events (Patients 90107 and 90109[§§§§§§§§§]).

All of these events occurred in patients with a diagnosis or evidence of renal disease at baseline (proteinuria, glomerulonephritis, chronic renal failure). In FHA101, there were no events relevant to chronic renal disease reported in the 28 patients.

[§§§§§§§§§] Patient 90109 died of liver and renal failure 9 months after discontinuing metreleptin.

Table 55. Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to Chronic Renal Disease

Patient ID Age / Sex / Type	Relevant Medical History (Baseline 24-hr Urine Protein)	Verbatim Term	Time to Onset (Days)	SAE?
90106 35 / F / CGL	Proteinuria (2.8g/24h)	Proteinuria Kidney failure	65 3464	N Y - fatal
90107 42 / F / FPL	Focal glomerulonephritis, stage IV kidney failure, proteinuria (1.9g/24h)	End stage renal disease Right renal transplant	2519 (approx.) 2748	N Y
90109 13 / F / AGL	Proteinuria (2.7g/24h)	Membranoproliferative glomerulonephritis Worsening of proteinuria	441 422	N Y
90113 12 / F / CGL	Proteinuria (3.2g/24h)	Focal proliferative glomerular sclerosis	327 (approx.)	N
90114 35 / M / AGL	Chronic renal failure, proteinuria (2.5g/24h)	Membranoproliferative glomerulonephritis Worsening of proteinuria	270 270	N N[1]
90163 20 / F / CGL	Proteinuria (5.5g/24h)	Focal segmental glomerulosclerosis	136	N

[1] AE led to withdrawal, although the patient was subsequently enrolled in a compassionate use program in her country

Source: Clinical Safety Update, Table 42; Response to FDA Request for Information Dated 08-Oct-2013, Table 3

Proteinuria, Creatinine, and BUN

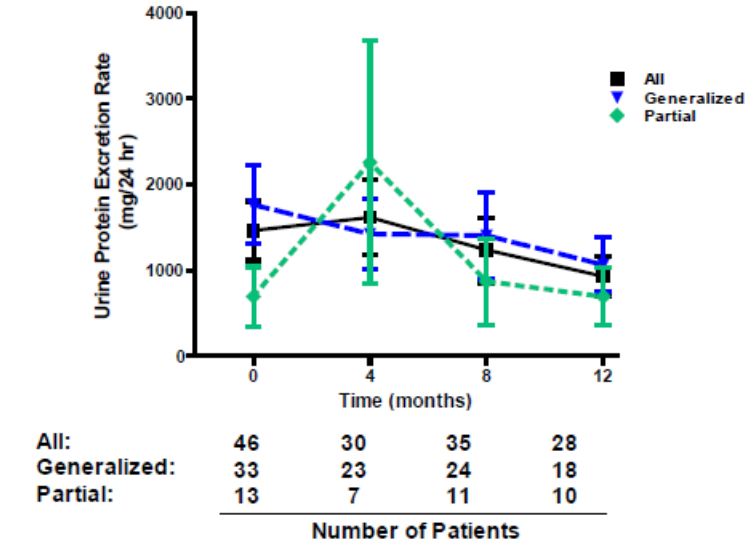
The NIH published[30] a 15-patient subset with generalized lipodystrophy evaluating proteinuric nephropathy in lipodystrophy patients.********** Of these 15 patients, it was reported that 11 (73%) had a reduction in proteinuria with treatment.

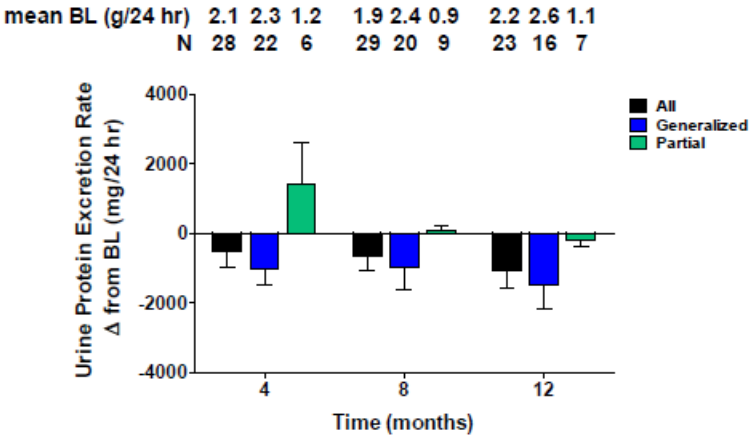
Reviewer comments: Note that two patients presented in the table above and also in the cited NIH publication, 90109 and 90114, had worsening of proteinuria. As described in other sections of this review, the contribution of metreleptin to the worsening of MPGN in these two patients cannot be excluded.

Mean changes from the available 24-hour urine protein measurements are presented in the figure below. The increase in the 24-hour urine protein was observed at Month 4 among patients with partial lipodystrophy was driven by the results in Patient 90107 who had an increase in 24-hr urine protein from 1.9 g/24 hr at baseline to 9.1 g/24 hr at Month 4, but eventually had a decreased 24-hr urine protein value with continued therapy.

********** Discrepancies were found between the publication and the BLA in baseline data (age and HbA1c) for patients 90105, 90106, 90122.

Figure 26. Mean (SE) 24-Hour Urine Protein Concentrations Over Time and Change From Baseline at Month 4, 8, and 12; NIH Trials





BL = baseline.

Source: Clinical Safety Update, Figure 1

Reviewer comments: Despite the sponsor's contention that metreleptin improves proteinuria, there appears to be a number of patients who developed worsening proteinuria or creatinine during the trial (see Table 56 below). It is plausible that the reduction in proteinuria reflects decreased glomerular hyperfiltration, but whether this is the result of a metreleptin-mediated metabolic process or other confounders (e.g., reductions in blood pressure, addition or intensification of relevant concomitant medications) cannot be determined. Furthermore, whether a treatment-associated reduction in proteinuria will translate into a benefit on

renal outcomes (i.e., irreversible loss of renal function and progression to ESRD) for the heterogeneous collection of renal diseases associated with lipodystrophy is unknown.

Limitations to the 24-hour urine protein assessments include: (1) urine creatinine was not reported, and (2) changes in concomitant medications (e.g., ACE-inhibitors, angiotensin receptor blockers) or blood pressure can affect proteinuria markedly; these factors were not controlled for in the trial.

The table below lists the patients who had an increase in creatinine of 0.3 mg/dL or greater at two or more consecutive visits (n = 5), and those who had an increase in 24-hr urine protein of 1 g or greater at least one time (n = 8) or at two or more consecutive visits (n = 2) or 2 g or greater at least one time (n = 5). No patients had an increase in 24-hr urine protein of 2 g or greater at two or more consecutive visits. With the exception of Patient 90112, who had a history of hypertension but without documented renal disease and no assessment of 24-hr urine protein at baseline, these patients had a history of renal disease or evidence of renal disease (i.e., proteinuria) at baseline.

Reviewer comment: Given the limitations to the medical history data, the proportion of patients who had baseline renal abnormalities and remained stable (or "improved") is unknown.

The most notable increases in creatinine occurred in four patients with renal disease at baseline: Patient 90102[††††††††††] with a history of focal segmental glomerulosclerosis and massive proteinuria at baseline; Patient 90106[‡‡‡‡‡‡‡‡‡‡] with proteinuria at baseline who eventually died of chronic renal failure; Patient 90107 with a history of glomerulonephritis, stage IV kidney failure[§§§§§§§§§§], and proteinuria at baseline; and Patient 90114 with proteinuria at baseline who was diagnosed with MPGN within the first eight months of treatment and withdrawn due to worsening proteinuria (see the

[††††††††††] The increases in creatinine and proteinuria in Patient 90102 were not captured as adverse events. This case is described further in an NIH publication[30] as follows: *Patient [90102] is a 17-yr-old female with CGL. She had a baseline urinary protein excretion of 11 g/24 h and a creatinine clearance of 73 ml/min. She was known to have proteinuria since age 11 yr, and a kidney biopsy done 2 yr before initiating leptin therapy revealed focal segmental glomerulosclerosis (FSGS). She was treated with leptin over an 18-month period during which she had a slow, but progressive, deterioration of renal function. There was an initial fall in urinary protein excretion that was not sustained. Leptin therapy was discontinued after 30 months as she approached end-stage renal disease.*

[‡‡‡‡‡‡‡‡‡‡] This patient initiated metreleptin treatment on 08 Sep 2000 but experienced an adverse event on the second day of treatment, and metreleptin was discontinued. She re-initiated metreleptin on 19 Sep 2000 but again discontinued one day later after she experienced another adverse event. Metreleptin was restarted on 15 Nov 2000, which was used as her modified first dose date for efficacy analyses. True baseline labs (prior to the first dose date on 08 Sep 2000) were not provided in the BLA, but the sponsor verified that a true baseline value for 24-hr urine protein is available for this patient (dated 07 Sep 2000): 2.8 g/24 hr (note the discrepancy between this value and the table below).

[§§§§§§§§§§] As reported in the table below; although it is noted that the patient's baseline creatinine was 1.6 mg/dL, which is consistent with an eGFR of ~40 mL/min (stage 3 CKD).

narrative for this patient's adverse event in Section 7.3.3, Dropouts and/or Discontinuations).

Table 56. Individual Patient Listing of Creatinine and 24-hr Urine Protein Increases Meeting Categorical Criteria (NIH Trial)

Patient ID / Demog	Relevant Medical History	Serum Creatinine (mg/dL)		24-hr Urine Protein (g/24 hr)			Summary of Post-Baseline 24-hr Urine Protein Values
		Incr ≥0.3 at least 2 times	Baseline to Last Available	Incr ≥1 g/24hr at least once	Incr ≥1 g/24 hr at least 2 times	Incr ≥2 g/24hr at least once	
90102 17 yr F, CGL	Focal segmental glomerulosclerosis, proteinuria (>11 g/24 hr)	X	1.4 to 2.9 (Month 16)	X		X	Proteinuria decreased to 3.3 g (Month 16), increased to >11 and >15 g (Year 2)
90106[1] 35 yr F, CGL	Proteinuria (2.6 g/24 hr)		0.7 to 2.8 (Year 9)				Proteinuria decreased to 616 mg (Month 10) and increased back to 2.3 g (Year 9)
90107 42 yr F, FPL	Focal glomerulonephritis, stage IV kidney failure, proteinuria (1.9 g/24 hr)	X	1.6 to 4.7 (Year 6), 0.9 after renal transplant	X		X	Proteinuria fluctuated (min 256 mg prior to renal transplant, max 9.1 g, final 161 mg)
90109 13 yr F, AGL	Proteinuria (2.7 g/24 hr)		0.3 to 0.5 (Month 16), max 0.6	X		X	Proteinuria decreased to 1.2 g, increased to 20 g final visit (SAE)
90110[1] 8 yr F, AGL	Mild proteinuria (390 mg to 1.5 g/24 hr) Kawasaki's disease		0.6 to 0.59 (Year 7), max 0.95	X			Proteinuria decreased to ~200 mg (Year 3)
90111 13 yr M, CGL	Proteinuria (252 mg/24 hr)	X	0.6 to 0.95 (Year 8), max 1.11				Proteinuria fluctuated (min 84 mg, max 567 mg, final 272 mg)
90112 64 yr F, FPL	Hypertension, baseline 24-hr urine protein not available	X	0.7 to 1.17 (Year 9), max 1.47				24-hr urine protein 95 mg (Month 30) and 206 mg (Year 7)
90113 12 yr F, CGL	Proteinuria (3.2 g/24 hr)		0.3 to 0.46 (Year 6), max 0.5	X		X	Proteinuria fluctuated (min 1 g, max 5.7 g, final 3.6 g)
90114 35 yr M, AGL	Chronic renal failure, proteinuria (2.45 g/24 hr)	X	1 to 2.2 (Month 8)	X	X	X	Proteinuria increased to 4.1 g (Month 4) and 8.9 g (Month 8)
90132 18 yr F, APL	Focal segmental glomerulonephritis, nephropathy, proteinuria (4.5 g/24hr)		0.2 to 0.3 (Year 1)	X	X		Proteinuria increased to 6 g (Month 4), decreased to 3 g (Year 1)
90137 13 yr F, CGL	Proteinuria (457 mg/24 hr), hypertension		0.5 to 0.69 (Year 4), max 0.8	X			Proteinuria increased to 1.9 g (Year 1), decreased to 1.2 g (Year 2)

Incr = increase; Yr = years; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.
[1] Modified first dose date due to on and off therapy.
Source: Clinical Safety Update, Table 26

One additional event of proteinuria was reported after the data cutoff for the BLA submission. Patient 90134, a 9-year-old male at study entry with CGL, experienced

worsening proteinuria approximately 5.5 years after initiating metreleptin treatment. The patient had a medical history of proteinuria (baseline 24-h urine protein 175.7 mg). At the time of the event, 24-h urine protein increased to 723.5 mg. At the final visit (at the time of data cutoff), 24-h urine protein had decreased slightly to 587.3 mg. The event was ongoing as of the 11 Jan 2013 data cutoff and was being treated with ramipril.

Although the evaluation is limited due to the fact that the sample size changes over time, there are potential renal function changes over time in this population, as well as no comparator group available, descriptive statistics of mean changes in BUN and creatinine by visit are presented below.

Reviewer comment: Mean values of BUN and creatinine were all well within normal, although a small increase in creatinine was seen over time, of unknown significance (note that there are only 2-3 patients' data available after Year 7).

Table 57. BUN Values and Change from Baseline by Visit

Parameter/Visit	n	Mean (SD)	SE	Median	Min	Max
BUN (mg/dL)						
Baseline [1]	72	12.26 (5.874)	0.692	11.00	2.0	38.0
Month 4	46	11.96 (5.573)	0.822	12.00	1.2	35.0
Month 8	54	12.04 (6.025)	0.820	11.00	2.0	32.0
Year 1	52	12.02 (5.599)	0.776	10.50	4.0	32.0
Year 2	26	12.54 (6.872)	1.348	11.00	5.0	35.0
Year 3	21	12.67 (6.288)	1.372	12.00	4.0	25.0
Year 4	17	14.35 (9.701)	2.353	12.00	5.0	38.0
Year 5	16	16.13 (10.269)	2.567	12.50	5.0	41.0
Year 6	12	12.92 (4.776)	1.379	12.00	6.0	22.0
Year 7	3	14.67 (7.024)	4.055	14.00	8.0	22.0
Year 8	2	14.50 (6.364)	4.500	14.50	10.0	19.0
BUN (mg/dL) - Change from Baseline [1]						
Month 4	46	-0.82 (4.514)	0.666	0.00	-18.0	6.0
Month 8	54	-0.30 (4.769)	0.649	-1.00	-12.0	14.0
Year 1	52	-0.15 (3.664)	0.508	0.00	-8.0	11.0
Year 2	26	-0.27 (4.788)	0.939	0.00	-12.0	8.0
Year 3	21	-0.71 (5.081)	1.109	0.00	-15.0	11.0
Year 4	17	0.29 (4.089)	0.992	1.00	-6.0	9.0
Year 5	16	1.88 (3.845)	0.961	2.50	-4.0	9.0
Year 6	12	1.42 (3.204)	0.925	1.50	-2.0	8.0
Year 7	3	2.00 (3.606)	2.082	1.00	-1.0	6.0
Year 8	2	2.00 (1.414)	1.000	2.00	1.0	3.0

[1] In general, baseline measurement is defined as the last available value before the subject received the first injection of metreleptin.

Source: Clinical safety Update, Supporting Data Summary 3.3.1.3

Table 58. Creatinine Values and Change from Baseline by Visit

Parameter/Visit	n	Mean (SD)	SE	Median	Min	Max
Creatinine (mg/dL)						
Baseline [1]	69	0.61 (0.270)	0.032	0.58	0.2	1.6
Month 4	46	0.63 (0.294)	0.043	0.60	0.2	1.6
Month 8	54	0.62 (0.348)	0.047	0.53	0.2	2.2
Year 1	52	0.62 (0.310)	0.043	0.56	0.2	1.8
Year 2	26	0.74 (0.527)	0.103	0.60	0.3	2.9
Year 3	21	0.70 (0.336)	0.073	0.60	0.3	1.9
Year 4	17	0.77 (0.420)	0.102	0.60	0.4	2.2
Year 5	16	0.80 (0.502)	0.125	0.76	0.4	2.5
Year 6	12	0.65 (0.232)	0.067	0.65	0.4	1.0
Year 7	4	0.80 (0.249)	0.124	0.76	0.6	1.1
Year 8	2	0.61 (0.028)	0.020	0.61	0.6	0.6
Creatinine (mg/dL) - Change from Baseline [1]						
Month 4	44	0.03 (0.141)	0.021	0.00	-0.3	0.6
Month 8	52	0.04 (0.201)	0.028	0.00	-0.2	1.2
Year 1	51	0.01 (0.136)	0.019	0.00	-0.2	0.4
Year 2	26	0.10 (0.321)	0.063	0.06	-0.2	1.5
Year 3	21	0.10 (0.167)	0.037	0.13	-0.2	0.3
Year 4	17	0.14 (0.178)	0.043	0.20	-0.2	0.6
Year 5	16	0.18 (0.250)	0.062	0.17	-0.2	0.9
Year 6	12	0.12 (0.172)	0.050	0.13	-0.2	0.3
Year 7	4	0.25 (0.127)	0.063	0.24	0.1	0.4
Year 8	2	0.21 (0.028)	0.020	0.21	0.2	0.2

[1] In general, baseline measurement is defined as the last available value before the subject received the first injection of metreleptin.

Source: Clinical Safety Update, Supporting Data Summary 3.3.1.3

Obesity and Investigator-Initiated Trials

In the five integrated obesity trials in the Amgen ISS, there were no adverse events suggestive of nephropathy or renal insufficiency. In metreleptin-treated patients, mean changes from baseline to the last post-baseline assessment were 0.0 mg/dL (as compared to -0.01 mg/dL for placebo) for serum creatinine.

The following renal-related adverse events were reported by the sponsor for the Amgen trials not included in the ISS as well as the metreleptin + pramlintide for obesity clinical program (no further details were provided):

Of the renal adverse events, there were 17 reports of creatine phosphokinase elevated in metreleptin-treated subjects and six in placebo-treated subjects. In addition, there was a single report of azotemia and one report each of hypercalcemia and hypocalcemia in metreleptin-treated patients. The remaining events appeared to be related to either urinary tract infections or frequent urination. All of these events were distributed across the various studies and appeared in a similar incidence in metreleptin and placebo-treated subjects.

Finally, a serious case of diabetic nephropathy and tubulointerstitial nephritis was reported in a patient with CGL who had been receiving metreleptin in an investigator-initiated trial for approximately 10 years; see below.

Table 59. Individual Patient Data for Patients with Renal-related Serious Adverse Events: Metreleptin in Compassionate-Use and Investigator-Initiated Trials

INVESTIGATOR-INITIATED TRIALS				
Indication: LD				
Study ID / Demographics	**Relevant Medical History**	**SAEs**	**Time to Onset**	**Relevant comments**
20020701 30 yr, M, CGL	CGL, diabetes, neurogenic bladder, hepatic steatosis, UTI, diabetic nephropathy, mood disorder	**Diabetic nephropathy** **Tubulointerstitial nephritis** **Hyperkalaemia**	Approximately 10 years	Kidney biopsy showed advanced diabetic nephropathy with chronic interstitial nephritis. Recurrent hyperkalemia secondary to acute renal injury.

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-9

Cardiovascular-Related Adverse Events

Patients with lipodystrophy have elevated TG concentrations, hyperinsulinemia (often with diabetes mellitus), and low levels of HDL-C, which are associated with an increased risk for cardiovascular disease;[31] in particular, patients with Dunnigan-type FPL (*LMNA* mutations).[32] In addition, some patients with lipodystrophy may present with cardiomyopathy or rhythm defects.[31]

The role of leptin on the cardiovascular system has been reviewed (see reference 33); the authors note that elevated serum leptin has been associated with cardiovascular disease including stroke, chronic heart failure, acute myocardial infarction, coronary heart disease, and left cardiac hypertrophy. Nevertheless, observational data can be confounded by the multitude of risk factors that occur in patients with obesity and elevated leptin concentrations.

Experiments in several different rodent models have shown that leptin regulates blood pressure via sympathetic activation, and that hyperleptinemia in obesity can result in hypertension. Further, the mechanisms through which leptin regulates blood pressure, via stimulation of renal sympathetic nerve activity, appear to be intact in the presence of resistance to the weight reducing effects of leptin, supporting the concept of selective central leptin resistance in obesity.[33] Under physiological conditions leptin induces endothelium-dependent vasorelaxation by stimulating nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF). However, at supratherapeutic concentrations, there is evidence that the endothelium becomes resistant to the vasodilating effects of leptin.[34]

Reviewer comment: It is unclear what the impact of replacement or pharmacological doses of metreleptin would be on the endothelium in a leptin-deficient state (and the impact of leptin-deficiency on the vasculature in lipodystrophy).

Patients Treated for Lipodystrophy

In the NIH trials, two (2.8%) patients had a medical history of coronary artery disease, and four (5.6%) patients had cardiomyopathy (n = 2 with hypertrophic cardiomyopathy, n = 1 with cardiomyopathy, and n = 1 with decreased ejection fraction). In the FHA101 trial, seven (28%) of 25 patients with medical history captured had cardiovascular disease (n = 4 with coronary artery disease, n = 1 with aortic atherosclerosis, n = 1 with myocardial infarction, n = 1 with ischemic cardiomyopathy).

Reviewer comment: The discrepancy in cardiovascular disease is likely due to the high proportion of adults (with FPL) in the FHA101 trial. By contrast, over half of the patients in the NIH trials were less than 18 years of age.

In the NIH trials, adverse events in the *Cardiac Disorders* SOC were reported in three (4.2%) of 72 lipodystrophy patients and are summarized in the table below, along with other adverse events relevant to the cardiovascular system but coded under other SOCs (i.e., *General*, *Vascular*, *Investigations*). One adverse event in the *Cardiac Disorders* SOC had a fatal outcome (Patient 90125, cardiac arrest) in the setting of pancreatitis and septic shock (see Section 7.3.1, Deaths). The serious adverse event of worsening hypertension (Patient 90105) was assessed as related; see Section 7.3.2, Nonfatal Serious Adverse Events. In addition, a non-serious adverse event of chest pain (Patient 90106) was assessed as related. No further information on this adverse event of chest pain in Patient 90106 is available. There were no cases of congestive heart failure reported in the NIH trials.

In FHA101, no adverse events in the *Cardiac Disorders* SOC were reported, but two events of chest pain (*General Disorders* SOC) and two events of increased blood pressure (*Investigations* SOC), one of which occurred in a patient with an adverse event of chest pain, were reported. There were no cases of congestive heart failure reported in FHA101.

Table 60. Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to the Cardiovascular System, NIH and FHA101 Trials

Patient ID / Demog	Relevant Medical History	TEAE[1] (SOC)	Time to Onset (Days)	Investigator Assessment of Relatedness / SAE
NIH Studies 991265/20010769				
90101 17 yr F, AGL	Pancreatitis, diabetes mellitus, hypertriglyceridemia, steatohepatitis, anxiety	Palpitations Tricuspid valve incompetence (both Cardiac)	2006 349	Unrelated – non SAE Unrelated – non SAE
90105 14 yr F, CGL	Tachycardia, hypertension, diabetes, steatohepatitis, proteinuria Baseline BP 149/85, HR 105	Worsening of hypertension (Vascular) Tachycardia associated with worsening of hypertension (Cardiac)	0[2] 0[2]	Related – SAE Related – Non SAE
90106 35 yr F, CGL	Endocarditis, peripheral vascular disease, amputated left great toe, diabetes, hyperlipidemia, deep vein thrombosis, smoking, avascular necrosis, left shoulder pain	Chest pain (General)	11	Related – Non SAE
90107 42 yr F, FPL	Coronary artery disease, multiple stent placements, stable angina, hypertension, hypertriglyceridemia, diabetes mellitus, focal glomerulo-nephritis, stage IV kidney failure, proteinuria, recurrent pancreatitis	Cardiac catherization (Investigations)	2657	Unrelated SAE
90110 8 yr F, AGL	Asthma, Kawasaki's disease, hypertriglyceridemia, diabetes, mild proteinuria	Chest tightness (General)	194	Unrelated SAE
90111 13 yr M, CGL	Diabetes, proteinuria, diabetic retinopathy	Persistent recurrent chest pain (General)	242	Unrelated – Non SAE
90125 15 yr F, CGL	Hypertension, diabetes, pancreatitis, hyperlipidemia, baseline TG 1669 mg/dL, focal segmental glomerulosclerosis	Cardiac arrest (Cardiac)	106	Unrelated fatal SAE
90163 20 yr F, CGL	Hypertriglyceridemia, insulin resistance, polycystic ovary disease, fatty liver, proteinuria	Hypertension (Vascular)	135	Unrelated – Non SAE
Study FHA101				
648003 58 yr F, FPL	Coronary artery disease, hypertension, CABG, GERD, fatty liver, back and neck pain, lipid abnormalities, diabetes, hyperthyroidism	Chest pains (General)	500	Unrelated SAE
648013 23 yr F, FPL	Hypertension, increased cholesterol, increased triglycerides, diabetes, fatty liver, hyperandrogenism	Blood pressure elevation (Investigations)	364[3]	Unrelated – Non SAE
648019 55 yr F, FPL	High cholesterol, hypertension, ablation for supraventricular tachycardia (aberrant pathway), high cholesterol, high triglycerides, asthma, fatty liver, myopathy	Increased blood pressure (Investigations) Chest pain (General)	112 136	Related– Non SAE Unrelated – Non SAE

Yr = years; F = female; M = male; TG = triglycerides; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy; LFT = liver function tests; TEAE = treatment-emergent adverse event; SOC = system organ class.

[1] Verbatim.
[2] Event occurred after first injection of metreleptin treatment.
[3] Start day unknown, calculation based on the 1st of the month and year.

Source: Clinical Safety Update, Table 44

The following table summarizes the change in systolic and diastolic blood pressure in those patients with available data up to one year of metreleptin treatment as well as for patients with elevated baseline values (SBP 130 mmHg or greater, DBP 90 mmHg or greater).

Table 61. Mean Change from Baseline in Systolic and Diastolic Blood Pressure by Visit, NIH Trials

SBP	All Patients			Baseline SBP ≥130 mmHg		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	62	128.0	NA	26	143.0	NA
Month 4	35	130.1	-5.6	14.	146.9	-9.6
Month 8	41	129.8	-7.5	18	144.3	-15.3
Month 12	33	127.7	-7.1	12	141.8	-17.3
DBP	**All Patients**			**Baseline DBP ≥90 mmHg**		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	62	71.3	NA	6	92.3	NA
Month 4	35	71.9	-2.5	4	92.5	-12.0
Month 8	41	71.8	-1.6	3	92.3	-17.3
Month 12	33	70.4	+1.0	2	93.5	-13.5

BL = baseline; SBP = systolic blood pressure; DBP = diastolic blood pressure.
In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin.
Baseline blood pressure values are shown only for those patients who had blood pressure data at a certain time point.

Source: Clinical Safety Update, Table 29

Reviewer comment: As noted previously (reviewer comment) regarding evaluating a subset of patients with higher baseline values for the efficacy parameters, the observation of greater decreases from baseline might be expected in this select population (i.e., regression to the mean). The increased decreases from baseline observed in the subgroups with elevated SBP and DBP should therefore be interpreted with caution.

For those NIH patients with available baseline heart rate data (63 of 72), the mean (± SD) baseline heart rate was 92 (± 15.3) bpm. Mean (± SE) decreases from baseline in heart rate during the first year of treatment were -6.9 (± 2.2) bpm at Month 8 (n = 43) and -2.4 (± 3.1) bpm at Year 1 (n = 33).

The following table lists the patients having increases in systolic and diastolic blood pressure 10 mmHg or greater or 15 mmHg or greater at two or more consecutive visits. Two patients (90129, 90130) meeting the criteria for increases in both systolic blood pressure and diastolic blood pressure by greater than or equal to 10 and 15 mmHg for two or more consecutive times also met criteria for systolic BP 20 mmHg or greater for

two or more consecutive times. No patients had increase in diastolic blood pressure 20 mmHg or greater at two or more consecutive visits.

Table 62. Categorical Summary of Increases in Vital Sign Measurements, NIH Trials

Vital Sign Category	Generalized Lipodystrophy n (%) [RPY]	Partial Lipodystrophy n (%) [RPY]	All Patients n (%) [RPY]
Heart Rate (beats/min)			
N with a BL and at least 1 post-BL measurement	**39**	**20**	**59**
Increased by ≥5 bpm from BL at least 1 time	21 (53.8) [0.226]	9 (45.0) [0.145]	30 (50.8) [0.194]
Increased by ≥10 bpm from BL at least 1 time	12 (30.8) [0.107]	8 (40.0) [0.122]	20 (33.9) [0.112]
Increased by ≥15 bpm from BL at least 1 time	8 (20.5) [0.062]	5 (25.0) [0.071]	13 (22.0) [0.065]
Increased by ≥20 bpm from BL at least 1 time	3 (7.7) [0.019]	3 (15.0) [0.037]	6 (10.2) [0.025]
N with a BL and at least 2 post-BL measurements	**34**	**19**	**53**
Increased by ≥5 bpm from BL at 2 or more consecutive visits	6 (17.6) [0.043]	6 (31.6) [0.087]	12 (22.6) [0.057]
Increased by ≥10 bpm from BL at 2 or more consecutive visits	3 (8.8) [0.019]	2 (10.5) [0.024]	5 (9.4) [0.021]
Increased by ≥15 bpm from BL at 2 or more consecutive visits	1 (2.9) [0.006]	2 (10.5) [0.024]	3 (5.7) [0.012]
Increased by ≥20 bpm from BL at at least 2 consecutive visits	1 (2.9) [0.006]	2 (10.5) [0.024]	3 (5.7) [0.012]
Systolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**39**	**20**	**59**
Increased by ≥5 mmHg from BL at least 1 time	20 (51.3) [0.213]	11 (55.0) [0.198]	31 (52.5) [0.207]
Increased by ≥10 mmHg from BL at least 1 time	15 (38.5) [0.111]	8 (40.0) [0.123]	23 (39.0) [0.115]
Increased by ≥15 mmHg from BL at least 1 time	9 (23.1) [0.059]	8 (40.0) [0.121]	17 (28.8) [0.078]
Increased by ≥20 mmHg from BL at least 1 time	8 (20.5) [0.051]	3 (15.0) [0.040]	11 (18.6) [0.048]
N with a BL and at least 2 post-BL measurements	**34**	**19**	**53**
Increased by ≥5 mmHg from BL at 2 or more consecutive visits	6 (17.6) [0.042]	7 (36.8) [0.111]	13 (24.5) [0.063]
Increased by ≥10 mmHg from BL at 2 or more consecutive visits	4 (11.8) [0.026]	4 (21.1) [0.052]	8 (15.1) [0.035]
Increased by ≥15 mmHg from BL at 2 or more consecutive visits	2 (5.9) [0.013]	3 (15.8) [0.037]	5 (9.4) [0.021]
Increased by ≥20 mmHg from BL at 2 or more consecutive visits	1 (2.9) [0.006]	1 (5.3) [0.012]	2 (3.8) [0.008]
Diastolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**39**	**20**	**59**
Increased by ≥5 mmHg from BL at least 1 time	24 (61.5) [0.270]	15 (75.0) [0.434]	39 (66.1) [0.316]
Increased by ≥10 mmHg from BL at least 1 time	14 (35.9) [0.110]	11 (55.0) [0.205]	25 (42.4) [0.138]
Increased by ≥15 mmHg from BL at least 1 time	7 (17.9) [0.047]	5 (25.0) [0.067]	12 (20.3) [0.054]
Increased by ≥20 mmHg from BL at least 1 time	5 (12.8) [0.031]	3 (15.0) [0.037]	8 (13.6) [0.033]
N with a BL and at least 2 post-BL measurements	**34**	**19**	**53**
Increased by ≥5 mmHg from BL at 2 or more consecutive visits	10 (29.4) [0.076]	7 (36.8) [0.110]	17 (32.1) [0.087]
Increased by ≥10 mmHg from BL at 2 or more consecutive visits	4 (11.8) [0.027]	4 (21.1) [0.056]	8 (15.1) [0.037]
Increased by ≥15 mmHg from BL at 2 or more consecutive visits	2 (5.9) [0.013]	2 (10.5) [0.025]	4 (7.5) [0.017]
Increased by ≥20 mmHg from BL at 2 or more consecutive visits	0 (0.0) [0.000]	0 (0.0) [0.000]	0 (0.0) [0.000]

BL = baseline.

Notes: [RPY] = Rate per Patient Year, derived by dividing n by patient years of exposure. If a patient had the event, their exposure is truncated at the time of first event.

- Baseline measurement is defined as the last available value before the patient received the first injection of metreleptin.

Source: Clinical Safety Update, Table 30

Table 63. Individual Patient Listing of Blood Pressure Increases at Two or More Consecutive Visits, NIH Trials

Patient ID / Demog	Relevant Medical History	Baseline BP (mmHg)	Systolic BP increase From Baseline for ≥2 Consecutive Visits (mmHg)		Diastolic BP Increase From Baseline for ≥2 Consecutive Visits (mmHg)		Summary of Post-Treatment Measurements and Relevant AEs
			≥10 (n = 8)	≥15 (n = 5)	≥10 (n = 8)	≥15 (n = 4)	
90109 13 yr F, AGL	Diabetes, proteinuria	122/63 to 133/86 (M8)	X				BP increased to 136/72 mmHg at Month 2 (max), 132/70 mmHg at Month 4, and 133/86 mmHg at Month 8 (last available measurement).
90110 8 yr F, AGL	Diabetes, mild proteinuria, Kawasaki's disease	108/70 to 125/64 (Y 6.5)	X				BP generally in normal range except 139/77 mmHg at Year 5 (max). BP 121/69 mmHg at Year 6, and 125/64 mmHg at last visit at Month 78.
90113 12 yr F, CGL	Diabetes Proteinuria (on Ramipril)	129/63 to 134/74 (Y6)			X		BP generally in borderline range. At Month 12 and 18, BP was 127/74 mmHg and 126/74 mmHg. BP was 137/79 mmHg at Month 30 (max DBP), 142/72 at Month 36 (max SBP) 130/74 mmHg at Month 42, and 134/74 mmHg at Year 6. Developed focal segmental glomerulosclerosis around Y1.
90117 45 yr F, FPL	Hypertension (on metoprolol)	116/62 to 122/67 (Y8)			X		BP generally in normal to borderline range. At Month 30 and 36, BP was 120/78 mmHg (max DBP) and 136/72 mmHg (max SBP). BP 122/65 mmHg at Year 6.
90120 23 yr F, CGL	Diabetes Anxiety Proteinuria	121/55 to 118/68 (Y8)			X	X	BP generally in normal range, and all DBP values within normal range. Maximum DBP 75 mmHg at Y2. At Month 60 and 71, BP was 126/71 mm Hg and 129/73 mmHg. At Year 6, BP 129/73 (max SBP).
90123 43 yr F, FPL	Hypertension Diabetes	98/58 to 113/58 (Y7)	X	X			All BP in normal range. At Y6 and Y7, BP was 115/60 (max SBP) and 113/58 mmHg.
90128 15 yr M, AGL	Diabetes Intermittent dehydration	96/58 to 134/84 (Y6)	X	X			BP generally normal for 4 years except125/73 at Y3. At Y4, BP 109/65. Then next BP (last available) at Y6 was 134/84 mmHg (max).
90129* 34 yr F, FPL	Hypertension Diabetic nephropathy	125/73 to 154/92 (Y2)	X	X	X	X	BP increased several months of treatment and remained elevated - 139/85 at M4, 152/79 at M8, 144/94 at M12 (max DBP), 160/92 at M12 (max SBP), 154/92 at Y2 (last available). No relevant TEAEs noted.
90130* 7 yr F, CGL	Hypertrophic cardiomyopathy Diabetes	117/59 to 118/69 (Y6)	X	X	X	X	BP normal first year. At Month 18, 24 and 30, BP was 129/74 mmHg, 140/80 mmHg and 140/71 mmHg. Subsequent to that, BP was generally in the normal range. No TEAEs reported.
90138 34 yr F, FPL	Diabetes Anxiety	127/67 to 114/67 (Y4.5)			X	X	BP generally in normal to borderline range. At Month 4 and 12, BP was 124/87 mmHg (max DBP) and 126/83 mmHg.
90141 10 yr F, APL	Diabetes	110/78 to 111/74 (Y3.5)	X				BP generally in normal to borderline range. At Month 8 and 12, BP was 126/71 mmHg (max SBP) and 123/77 mmHg. All other BP measurements normal.
90152 30 yr F, FPL	Preeclampsia Diabetes	134/77 to 141/88 (M18)			X		Only 2 post-treatment measures. At M8, BP was 134/89 mmHg, and at Month 18, BP was 141/88 mmHg.
90163 20 yr F, CGL	Nephromegaly Proteinuria Diabetes	144/75 to 144/89 (M18)			X		Hypertensive at baseline and BP remained in similar range. At Month 8 and 18, BP was 142/86 mmHg and 144/89 mmHg (max DBP). At M4, patient had a non SAE of hypertension (started on lisinopril) and also diagnosed with focal segmental glomerulosclerosis at same time.
90166 2 yr F, FPL	No relevant medical history	87/43 to 102/62 (Y1)	X	X			Only 2 post-treatment measures. At Month 8 and 12, BP was 105/48 and 102/62 mmHg.

Yr = years; BP = blood pressure; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.
*Also met criteria for SBP increase ≥20 mmHg at 2 or more consecutive visits

Source: Clinical Safety Update, Table 31

The following table lists the five patients having increases in heart rate 10 bpm or greater or 15 bpm or greater at two or more consecutive visits. The baseline and last available heart rate measurements for these patients were all in the normal range (less than 100 bpm).

Table 64. Individual Patient Listing of Heart Rate Increases at Two or More Consecutive Visits, NIH Trials

Patient ID / Demog	Relevant Medical History	Baseline to Last Available (BPM)	Heart Rate Increase From Baseline for ≥2 Consecutive Visits (BPM)		Summary of Post-Treatment Measurements and Relevant AEs
			≥10 (n = 8)	≥15 (n = 5)	
90109 13 yr F, AGL	Diabetes proteinuria	95 to 98 (M8)	X		HR 101 (M1), 108 (M2), 125 (M4)
90124 17 yr M, CGL	Diabetes	75 to 82 (Y6)	X		HR generally in 70-90 range. Maximum heart rate 91 (Y1)
90130 7 yr F, CGL	Hypertrophic cardiomyopathy Diabetes	86 to 89 (Y6)	X	X	HR 129 at M4 (max) and remained elevated 101-115 first 2 yrs. From Y3 to Y6, HR in 80-90s except 101 (Y5).
90144 10 yr F, APL	Hypertension	55 to 98 (Y3.5)	X	X	HR 103 at M8 (first measurement), all subsequent values >100, max 132 at M18, except 2 measurements of 98.
90157 30 yr F, FPL	Hypertension Pre-eclampsia Palpitations Diabetes	56 to 86 (Y2)	X	X	Only 2 post-treatment measures. 85 at Y1, 86 at Y2.

Yr = years; HR = heart rate; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.

Source: Clinical Safety Update, Table 32

The following table summarizes the change in systolic and diastolic blood pressure in those patients with available data up to two years of metreleptin treatment as well as for patients with elevated baseline values (SBP 130 mmHg or greater) in FHA101. There were no patients with baseline DBP 90 mmHg or greater.

Table 65. Mean Change from Baseline in Systolic and Diastolic Blood Pressure by Visit, FHA101

SBP	All Patients			Baseline SBP ≥130 mmHg		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	25	133.3	NA	15	142.4	NA
Month 1	24	133.3	-6.6	14	143.1	-7.9
Month 12	10	133.9	-6.6	7	142.6	-8.9
Month 24	6	130.5	-14.5	4	139.3	-21.5
DBP	**All Patients**			**Baseline DBP ≥90 mmHg**		
	n	BL	Change from BL	n	BL	Change from BL
Baseline	25	74.1	NA	0	NA	NA
Month 1	24	73.8	-3.2	0	NA	NA
Month 12	10	73.4	-3.1	0	NA	NA
Month 24	6	69.0	-3.3	0	NA	NA

BL = baseline; SBP = systolic blood pressure; DBP = diastolic blood pressure; NA = not applicable.
In general, baseline measurement was defined as the last available value before the patient received the first dose of metreleptin.
Baseline blood pressure values are shown only for those patients who had blood pressure data at a certain time point.

Source: Clinical Safety Update, Table 38

For those FHA101 patients with available baseline heart rate data (25 of 28), the mean (± SD) baseline heart rate was 79.2 (± 13.7) bpm. A small mean (± SE) decrease in heart rate was seen at Month 1 (-1.0 ± 2.0 bpm, n = 24); thereafter, the decrease was generally in the range of -4.0 bpm to -6.0 bpm to Month 33.

The following table presents categorical analyses of heart rate, systolic and diastolic blood pressure by increases of greater than or equal to 5, 10, 15, and 20 beats per minute (heart rate) or mmHg (systolic and diastolic blood pressure) at least one time or at two or more consecutive visits.

Table 66. Categorical Summary of Vital Signs Increases, FHA101

Vital Sign Category	Generalized Lipodystrophy (N = 5) n (%) [RPY]	Partial Lipodystrophy (N = 23) n (%) [RPY]	All Patients (N = 28) n (%) [RPY]
Heart Rate (beats/min)			
N with a BL and at least 1 post-BL measurement	**3**	**22**	**25**
Increased ≥5 bpm from BL at least 1 time	1 (33.3) [0.51]	13 (59.1) [0.96]	14 (56.0) [0.90]
Increased ≥10 bpm from BL at least 1 time	0 (0.0) [0.00]	10 (45.5) [0.59]	10 (40.0) [0.46]
Increased ≥15 bpm from BL at least 1 time	0 (0.0) [0.00]	5 (22.7) [0.21]	5 (20.0) [0.17]
Increased ≥20 bpm from BL at least 1 time	0 (0.0) [0.00]	2 (9.1) [0.08]	2 (8.0) [0.07]
N with a BL and at least 2 post-BL measurements	**3**	**19**	**22**
Increased ≥5 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	8 (42.1) [0.43]	8 (36.4) [0.34]
Increased ≥10 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	3 (15.8) [0.12]	3 (13.6) [0.10]
Increased ≥15 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Increased ≥20 bpm from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Systolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**3**	**22**	**25**
Increased ≥5 mm Hg from BL at least 1 time	1 (33.3) [0.51]	11 (50.0) [0.71]	12 (48.0) [0.68]
Increased ≥10 mm Hg from BL at least 1 time	1 (33.3) [0.51]	7 (31.8) [0.37]	8 (32.0) [0.38]
Increased ≥15 mm Hg from BL at least 1 time	1 (33.3) [0.22]	5 (22.7) [0.24]	6 (24.0) [0.24]
Increased ≥20 mm Hg from BL at least 1 time	0 (0.0) [0.00]	3 (13.6) [0.13]	3 (12.0) [0.11]
N with a BL and at least 2 post-BL measurements	**3**	**19**	**22**
Increased ≥5 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	5 (26.3) [0.24]	6 (27.3) [0.27]
Increased ≥10 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	4 (21.1) [0.17]	5 (22.7) [0.20]
Increased ≥15 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	2 (10.5) [0.08]	2 (9.1) [0.07]
Increased ≥20 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Diastolic Blood Pressure (mmHg)			
N with a BL and at least 1 post-BL measurement	**3**	**22**	**25**
Increased ≥5 mm Hg from BL at least 1 time	1 (33.3) [0.51]	13 (59.1) [0.98]	14 (56.0) [0.92]
Increased ≥10 mm Hg from BL at least 1 time	1 (33.3) [0.51]	5 (22.7) [0.23]	6 (24.0) [0.25]
Increased ≥15 mm Hg from BL at least 1 time	1 (33.3) [0.36]	0 (0.0) [0.00]	1 (4.0) [0.03]
Increased ≥20 mm Hg from BL at least 1 time	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
N with a BL and at least 2 post-BL measurements	**3**	**19**	**22**
Increased ≥5 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	3 (15.8) [0.13]	4 (18.2) [0.16]
Increased ≥10 mm Hg from BL at 2 or more consecutive visits	1 (33.3) [0.51]	0 (0.0) [0.00]	1 (4.5) [0.03]
Increased ≥15 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]
Increased ≥20 mm Hg from BL at 2 or more consecutive visits	0 (0.0) [0.00]	0 (0.0) [0.00]	0 (0.0) [0.00]

BL = Baseline.
Notes: [RPY] = Rate per Patient Year, derived by dividing n by patient years of exposure. If a patient had the event, their exposure is truncated at the time of first event.
-Baseline measurement is defined as the last available value before the patient received the first injection of metreleptin.
Source: Clinical Safety Update, Table 39

The following table presents an individual patient listing of increases in systolic and diastolic blood pressure (greater than or equal to 10 or 15 mmHg) at two or more consecutive visits.

Table 67. Individual Patient Listing of Blood Pressure Increases at Two or More Consecutive Visits, FHA101

Patient Number / Demog	Relevant Medical History	Baseline to Last Available (mmHg)	Systolic BP Increase From Baseline for ≥2 Consecutive Visits (mmHg)		Diastolic BP Increase From Baseline for ≥2 Consecutive Visits (mmHg)		Summary of Post-Treatment Measurements and Relevant AEs
			≥10 (n = 5)	≥15 (n = 2)	≥10 (n = 1)	≥15 (n = 0)	
648001 9 yr F, AGL	Increased QT interval, atenolol for increased heart rate, lisinopril for proteinuria	110/51 to 112/65 (M35)	X		X		SBP 90's-120's (max 126 at M33). DBP 50's-60's (max 67 at M28).
648009 57 yr F, FPL	Hypertension (on HCTZ, amlodipine and enalapril), diabetes, anxiety	135/67 to 130/73 (Y2)	X	X			At M6 and M 9, BP was 168/66 and 150/70 mmHg, and returned back to baseline at M21 and M24 (129/59 and 130/73). SBP 130's-160's (max 168 at M6). DBP 60's-70's.
648011 62 yr F, FPL	Hypertension (on amlodipine, lisinopril, metoprolol), CAD, diabetes, anxiety	134/74 to 132/72 (M18)	X	X			SBP 130's-150's (max 154 at M12). DBP 60's-80's.
648017 58 yr M, FPL	Ischemic cardiomyopathy (on lisinopril), 3 stents, ICD implanted, Diabetes	132/60 to 138/63 (M9)	X				SBP 130's-150's (max 149 at M3). DBP 60's (max 65 at M3).
648019 55 yr F, FPL	Hypertension (on lisinopril, spironolactone)	133/82 to 107/74 (M9)	X				At M2, BP was 143/88. Non SAE of 'blood pressure increased' at M3 (BP 146/94). BP subsequently decreased to below baseline.

Yr = years; BP = blood pressure; F = female; M = male; CGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; AGL = acquired generalized lipodystrophy.
Source: Clinical Safety Update, Table 40

No patient had increases in heart rate by greater than or equal to 15 or 20 bpm at two or more consecutive visits. Three patients (648011, 648019, 648021) had increases in heart rate of 10 bpm or greater at two or more consecutive visits. All three patients had a history of hypertension and were receiving anti-hypertensive treatment. The maximum heart rate for all three patients was less than 100 bpm.

Patients Treated for Obesity

In the five integrated obesity trials in the Amgen ISS, adverse events in the *Cardiac Disorders* SOC had a higher overall incidence in obese patients treated with metreleptin (n = 14, 1.8%) than obese patients treated with placebo (n = 1, 0.3%). Cardiac adverse

events in metreleptin-treated patients were distributed across the following preferred terms: angina (n = 4), aortic valve disease (n = 1), arrhythmia (n = 1), atrial fibrillation (n = 1), extrasystoles (n = 1), palpitations (n = 4), sinus tachycardia (n = 1), tachycardia (n = 3), and ventricular arrhythmia (n = 1). One placebo-treated patient had a cardiac adverse event of palpitations. Four patients (all metreleptin-treated) experienced a serious adverse event in the *Cardiac Disorders* SOC [preferred terms: angina pectoris (n = 2), atrial fibrillation, ventricular arrhythmia]. In addition, under the *Investigations* SOC, three serious adverse events were reported: irregular heart rate (one metreleptin-treated, one placebo-treated) and increased blood pressure (placebo-treated).

Reviewer comment: The imbalance in cardiac events between metreleptin and placebo is noted, however the individual preferred terms are from a variety of cardiac conditions, and do not necessarily point to any a single underlying cardiac diagnosis. The narrative for the serious adverse event of ventricular arrhythmia is presented in Section 7.3.2, Nonfatal Serious Adverse Events.

The incidence of categorical increases of heart rate, systolic and diastolic blood pressure were higher in the metreleptin treatment groups than in the placebo treatment group, however the differences were small.

Table 68. Patients Meeting Criteria for Categorical Vital Sign Analyses, Amgen Obesity ISS, N = 1072

		Placebo		All Metreleptin	
Vital Sign	Criteria	Patients Meeting Criteria at Least 1 Time N (%) [RPY]	Patients Meeting Criteria ≥2 Consecutive Times N (%) [RPY]	Patients Meeting Criteria at Least 1 Time N (%) [RPY]	Patients Meeting Criteria ≥2 Consecutive Times N (%) [RPY]
Heart Rate (beat/min)	Increase ≥10	148 (43.3) [1.91]	51 (15.5) [0.51]	352 (45.2) [2.35]	123 (16.3) [0.65]
	Increase ≥15	76 (22.2) [0.80]	18 (5.5) [0.17]	191 (24.6) [1.05]	44 (5.8) [0.21]
	Increase ≥20	40 (11.7) [0.39]	5 (1.5) [0.05]	87 (11.2) [0.43]	15 (2.0) [0.07]
Systolic BP (mm Hg)	Increase ≥10	165 (48.2) [2.21]	72 (22.0) [0.77]	386 (49.6) [2.79]	180 (23.8) [1.01]
	Increase ≥15	104 (30.4) [1.14]	25 (7.6) [0.24]	253 (32.5) [1.50]	87 (11.5) [0.44]
	Increase ≥20	59 (17.3) [0.59]	11 (3.4) [0.10]	142 (18.3) [0.74]	39 (5.2) [0.19]
Diastolic BP (mm Hg)	Increase ≥10	120 (35.1) [1.40]	48 (14.6) [0.48]	300 (38.6) [1.86]	115 (15.2) [0.60]
	Increase ≥15	55 (16.1) [0.55]	14 (4.3) [0.13]	128 (16.5) [0.66]	44 (5.8) [0.21]
	Increase ≥20	21 (6.1) [0.20]	4 (1.2) [0.04]	59 (7.6) [0.28]	18 (2.4) [0.08]

Source: Clinical Safety Update, Table 54

In metreleptin-treated patients, the mean changes from baseline to the last post-baseline assessment were -1.6 mmHg (versus -1.1 for placebo) for systolic blood

pressure, -1.1 mm Hg (versus -0.7 for placebo) for diastolic blood pressure, and -0.4 bpm (versus -1.2 for placebo) for heart rate.

In the Amgen and Amylin obesity trials not included in the ISS, the following adverse events related to the cardiovascular system were tabulated by the sponsor. No denominators were provided in this table; however, it appears 1228 patients were exposed to metreleptin and approximately 400 patients to placebo in the non-ISS obesity trials combined. Given that these trials varied significantly in terms of study duration and inclusion of a placebo arm, the sponsor has not attempted to conduct analyses of integrated data across trials.

The adverse event of 'cardiac arrest' was described in Section 7.3.2, Nonfatal Serious Adverse Events.

Table 69. Cardiovascular Adverse Events, Additional Obesity Trials (non-ISS)

Cardiovascular Adverse Events	Metreleptin	Placebo
Preferred Term		
Aneurysm	1	0
Cardiac arrest	1	0
Coronary artery disease	1	0
Cardiac enzyme elevated	1	0
Cardiac murmurs (type not specified)	4	2
Hypertension	8	3
Miscellaneous rhythm abnormalities (tachycardia, bradycardia, palpitations, etc.)	16	5
Peripheral ischemia	1	0

Source: Response to FDA Clinical Q1 (24 May 2013), Table 1.4.5

Psychiatric Adverse Events

Because metreleptin is a centrally-acting product that affects appetite, it is possible that it might impact other central sites that affect reward, mood, and behavior. Evaluations of neuropsychiatric function, including suicidality assessments, are recommended in the development of products to treat obesity.[35] Utilizing the 2013 data cutoff, 11% of patients in the NIH trials and 9% of patients in the FHA101 trial experienced a psychiatric adverse event. One adverse event each of panic reaction, paranoia, and suicidal ideation********** in the NIH trials and one adverse event of suicidal ideation in the FHA101 trials were considered serious. Narratives are presented in Section 7.3.2, Serious Adverse Events.

********** Note that the adverse event of "suicidal ideation" was in fact a suicide attempt (see Section 7.3.2, Nonfatal serious adverse events). This adverse event is miscoded.

Table 70. Psychiatric Disorders Adverse Events, NIH Trials (2013 Data Cut)

	N=90 n (%)
Psychiatric Disorders	10 (11.1)
Anxiety	3 (3.3)
Depression	2 (2.2)
Insomnia	2 (2.2)
Bipolar disorder	1 (1.1)
Hallucinations, mixed	1 (1.1)
Panic reaction	1 (1.1)
Paranoia	1 (1.1)
Suicidal ideation	1 (1.1)

Source: Four-Month Safety Update, Protocol 991265 and 20010769 Supporting Data Summary 3.2.1.3

Table 71. Psychiatric Disorders Adverse Events, FHA101 (2013 Data Cut)

	N=35 n (%)
Psychiatric Disorders	3 (8.6)
Anxiety	3 (8.6)
Suicidal ideation	1 (2.9)

Source: Four-Month Safety Update, FHA101 Supporting Data Summary 3.2.1

In the obesity trials, psychiatric adverse events overall were similar in the metreleptin- and placebo-treated groups. Slight imbalances of unknown significance (metreleptin greater than placebo) was seen for adverse events of depression (including depressed mood), and adverse events related to sleep (insomnia, sleep disorder, etc.).

Table 72. Adverse Events from Psychiatric Disorders SOC, ISS Data (Amgen Obesity Trials)

	Metreleptin N=784	**Placebo N=351**
Psychiatric Disorders	49 (6.3)	21 (6.0)
Insomnia	17 (2.2)	7 (2.0)
Depression	12 (1.5)	4 (1.1)
Anxiety	7 (0.9)	5 (1.4)
Depressed mood	7 (0.9)	1 (0.3)
Stress	3 (0.4)	2 (0.6)
Sleep disorder	3 (0.4)	0
Libido decreased	1 (0.1)	1 (0.3)
Nervousness	1 (0.1)	1 (0.3)
Tearfulness	1 (0.1)	1 (0.3)
Abnormal dreams	1 (0.1)	0
Emotional disorder	1 (0.1)	0
Initial insomnia	1 (0.1)	0
Mood swings	1 (0.1)	0
Terminal insomnia	1 (0.1)	0

Source: Reviewer-generated from ISS dataset (iss dae.xpt)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Patients Treated for Lipodystrophy

The following table presents the adverse events with incidence of 5% or greater in the 72 patients in order of decreasing incidence in the NIH trial. For comparison, the updated incidence from the four-month safety update (N = 90) is included, as well as the common adverse events from the FHA101 trial (N = 28) and four-month safety update (N = 35).

Reviewer comment: Pronounced differences in incidences of some adverse event preferred terms are noted in the NIH trials as compared with the FHA101 trial (Table 73). Some of the differences may be due the small numbers of patients; however, differences may also be attributed to the differences in the patient populations, the dosing algorithm, or ascertainment of adverse events between the trials / study sites.

Table 73. Frequent (Incidence 5% or Greater) Treatment-Emergent Adverse Events by Preferred Term in Patients Receiving Metreleptin, NIH and FHA101 Trials (with Four-Month Safety Update Data)

	NIH		FHA101	
Preferred Term	**BLA N=72 n (%)**	**4-month safety update N=90 n (%)**	**BLA N=28 n (%)**	**4-month safety update N=35 n (%)**
Hypoglycemia	8 (11.1)	10 (11.1)	7 (25.0)	12 (34.3)
Fatigue	7 (9.7)	7 (7.8)	2 (7.1)	2 (5.7)
Headache	6 (8.3)	7 (7.8)	2 (7.1)	3 (8.6)
Nausea	6 (8.3)	7 (7.8)	10 (35.7)	12 (34.3)
Weight decreased	6 (8.3)	13 (14.4)	2 (7.1)	2 (5.7)
Abdominal pain	5 (6.9)	10 (11.1)	5 (17.9)	5 (14.3)
Alopecia	5 (6.9)	6 (6.7)	0	0
Ovarian cyst	5 (6.9)	6 (6.7)	1 (3.6)	1 (2.9)
Pain in extremity	5 (6.9)	5 (5.6)	0	0
Upper respiratory tract infection	5 (6.9)	6 (6.7)	5 (17.9)	7 (20.0)
Arthralgia	4 (5.6)	7 (7.8)	0	0
Constipation	4 (5.6)	4 (4.4)	1 (3.6)	1 (2.9)
Diarrhea	4 (5.6)	4 (4.4)	0	0
Dizziness	4 (5.6)	4 (4.4)	2 (7.1)	3 (8.6)
Ear infection	4 (5.6)	5 (5.6)	1 (3.6)	3 (8.6)
Pancreatitis	4 (5.6)	5 (5.6)	0*	1 (2.9)*
Renal cyst	4 (5.6)	4 (5.6)	0	0
Decreased appetite	2 (2.8)	6 (6.7)	0	0
Urinary tract infection	2 (2.8)	2 (2.2)	6 (21.4)	6 (17.1)
Vomiting	2 (2.8)	3 (3.3)	5 (17.9)	5 (14.3)
Injection site hematoma	0	0	5 (17.9)	5 (14.3)
Injection site urticaria	1 (1.4)	1 (1.1)	4 (14.3)	4 (11.4)
Lymphadenopathy	0	0	4 (14.3)	4 (11.4)
Sinusitis	3 (4.2)	4 (4.4)	4 (14.3)	4 (11.4)
Muscle spasms	2 (2.8)	3 (3.3)	3 (10.7)	4 (11.4)
Myalgia	0	0	3 (10.7)	3 (8.6)
Anxiety	1 (1.4)	3 (3.3)	3 (10.7)	3 (8.6)
Back pain	3 (4.2)	3 (3.3)	2 (7.1)	2 (5.7)
Blood pressure increased	0	0	2 (7.1)	3 (8.6)
Chest pain	2 (2.8)	2 (2.2)	2 (7.1)	2 (5.7)
Cough	3 (4.2)	3 (3.3)	2 (7.1)	2 (5.7)
Increased appetite	0	0	2 (7.1)	2 (5.7)
Loss of consciousness	0	0	2 (7.1)	2 (5.7)
Musculoskeletal pain	1 (1.4)	1 (1.1)	2 (7.1)	2 (5.7)
Neuropathy peripheral	0	0	2 (7.1)	2 (5.7)
Vertigo	0	0	2 (7.1)	4 (11.4)
Viral infection	0	0	2 (7.1)	3 (8.6)
*Does not include 1 patient with “pancreatitis acute”				

Source: Clinical Safety Update, SDS 3.2.1.1; Clinical Safety Update, SDS 3.2.1; 4-Month Safety Update SDS 3.2.9; 4-Month Safety Update, SDS 3.2.1

Hypoglycemia is the most frequent adverse event in the NIH trial, and one of the most common in the FHA101 trial. This event is discussed in more detail in Section 7.3.5, Submission Specific Primary Safety Concerns.

All events of fatigue in the patients from the NIH trial were deemed of mild-to-moderate severity. Fatigue did not appear to be related to hypoglycemia, since only one patient (90116) who had an event of fatigue also had hypoglycemia (which occurred three months before the event of fatigue). Of note, fatigue was reported in the medical history of six (8.3%) of 72 patients.

In the NIH trial, nausea events were deemed mild or moderate intensity except for one event of severe intensity. Of eight nausea events, five had a duration from one to 11 days, and six had resolved by the data cutoff date for this submission (data on duration for three events and on resolution for two events are incomplete). None of the events of nausea occurred at the same time as an event of pancreatitis or an event related to the hepatobiliary system. In the FHA101 trial, nausea events were deemed to be of mild or moderate intensity except for one event of severe intensity, reported as a serious adverse event (along with severe vomiting and severe abdominal pain, Patient 677002, see Section 7.3.2, Serious Adverse Events). Of note, four (16%) of 25 patients with medical history captured in the FHA101 trial had a medical history of nausea.

Of 72 patients, six (8.3%) patients in the NIH trials experienced weight loss deemed by the investigator as an adverse event. [There was a mean (± SE) decrease in body weight of -2.0 (± 0.64) kg in patients with data at Year 1 of metreleptin treatment (n=49), with body weight generally remaining stable after the first year for the patients with data up to Year 6.] All six patients with adverse events of weight loss had generalized lipodystrophy. The following table summarizes baseline and last available body weight and BMI for these six patients, as well as the time to onset and metreleptin dose.

Table 74. Individual Patient Listing of Treatment-Emergent Adverse Events Relevant to Weight Loss, NIH Trials

Patient ID / Demog	Metreleptin Dose During Study	Measurements BW (kg)/BMI (kg/m$^{2)}$	TEAE [1] (SOC)	Time to Onset (Days)
90116 47 yr F, CGL	0.55 mg BID BL to 6.00 mg QD at Y9 (data cut off)	BW: 60.4 BL; 52.8 Y5 BMI: 22.9 BL; 20.6 Y5	Weight loss	243[2]
90120 23 yr F, CGL	0.80 mg BID BL to 5.50 mg QD at Y8 (data cut off)	BW: 80.6 BL, 53.8 Y6 BMI: 25.2 BL, 17.6 Y6	Weight loss	[3]
90128 15 yr M, AGL	0.2 mg BID BL to 2.50 mg BID at Y7 (data cut off)	BW: 59.1 BL, 52.0 M30 BMI: 21.6 BL, 18.7 M30	Weight loss	270
90150 11 yr M, AGL	2.75 mg QD BL to 3.20 QD at Y3 (data cut off)	BW: 46.3 BL; 46.7 M18; 53.7 M30. BMI: 20.0 BL; 18.4 M18, 19.9 M30;	Weight loss	1
90153 16 yr F, CGL	3.00 mg BID BL to 6.00 mg QD at Y2 (data cut off)	BW: 52.7 BL; 53.7 M4; 48.3 M18. BMI: 20.4 BL; 20.9 M4; 19.2 M18	Decreased appetite Weight loss	176[2] 176[2]
90162 11 yr F, AGL	2.90 mg QD BL to 4.20 mg QD at Y1 (data cut off)	BW: 36.8 BL; 38.2 M12; 33.6 M18. BMI: 14.4 BL; 14.4 M12; 12.5 M18	Decreased appetite Weight loss	216[2] 421

Yr = years; F = female; M = male; BL = baseline; BW = body weight; BMI = body mass index; QD = once daily; BID = twice daily; CGL = congenital generalized lipodystrophy; AGL = acquired generalized lipodystrophy; TEAE = treatment-emergent adverse event; SOC = system organ class.
Notes: Shaded rows indicate TEAEs that occurred between 31 July 2009 and 11 July 2011.
- Last body weight/BMI measurements reflect last available data.
[1] Verbatim.
[2] Start day unknown, calculation based on the 1st of the month and year.
[3] Onset date for the event is unknown; the event occurred in the same month the patient started metreleptin treatment.

Source: Clinical Safety Update, Table 18

Reviewer comment: Because weight loss could be considered a pharmacodynamic effect of the drug, I reviewed the efficacy (HbA1c and TG) findings in these patients, close to the onset of the weight loss adverse event, where known:

- ***Patient 90116: No improvement in HbA1c (7% to 7.2%) although insulin was discontinued; decrease in TG (1543 mg/dL to 160 mg/dL)***

- ***Patient 90120: Lowering of HbA1c and TG decreased by Month 4 and sustained (Month 12: HbA1c 8.7% to 4.5%, off insulin; TG 702 mg/dL to 109 mg/dL)***

- ***Patient 90128: Lowering of HbA1c and TG seen at Month 8 (approximate time of weight loss adverse event); however, he was reportedly only 50% compliant with metreleptin at that time (HbA1c 10.1% to 8.7%; TG 150 mg/dL to 96 mg/dL)***

- ***Patient 90150: No improvements [treatment still ongoing, but notably no baseline diabetes mellitus or hypertriglyceridemia (HbA1c 5% to 5.6% at Month 12; TG 141 mg/dL to 153 mg/dL at Month 12)]***

- ***Patient 90153: Lowering of HbA1c and TG was seen at Month 4 (approximate time of weight loss adverse event): HbA1c 11% to 7.8%; TG 872 mg/dL to 73 mg/dL***

- ***Patient 90162: Lowering of HbA1c and TG was seen at Month 12 (approximate time of weight loss adverse event); however, metformin was also started: HbA1c 7.8% to 5.6%, TG 337 mg/dL to 107 mg/dL***

In summary, weight loss may be associated with improvements in HbA1c and TG; however, this finding is variable.

Urinary tract infection (UTI) was the third most common adverse event in the FHA101 trial (21.4%), although it was not a frequent event in the NIH trials (2.8%). Of note, five (20%) of the 25 patients with medical history captured in the FHA101 trial had a medical history of UTI.

Patients Treated for Obesity

The following table summarizes frequent (incidence 5% or greater in any treatment group) adverse events from the three trials in obese patients and two trials in obese patients with type 2 diabetes in the ISS. The most frequently reported adverse event was injection site reaction, which occurred in 59.8% of metreleptin-treated patients versus 44.7% of placebo-treated patients. The next most frequently occurring adverse events (incidence greater than 10%) were headache (15.7% metreleptin versus 12.3% placebo) and nasopharyngitis (12.1% versus 12.5%).

Table 75. Frequent (Incidence 5% or Greater in Any Treatment) Adverse Events by Preferred Term in Obese Patients, ISS

	Placebo N=351	**Metreleptin N=784**
Any Adverse Event	299 (85.2)	724 (92.3)
Injection site reaction	157 (44.7)	469 (59.8)
Headache	43 (12.3)	123 (15.7)
Nasopharyngitis	44 (12.5)	95 (12.1)
Injection site erythema	2 (0.6)	85 (10.8)
Injection site pruritus	6 (1.7)	63 (8.0)
Fatigue	24 (6.8)	50 (6.4)
Influenza	24 (6.8)	48 (6.1)
Diarrhea	17 (4.8)	42 (5.4)
Nausea	17 (4.8)	42 (5.4)

Injection site inflammation	2 (0.6)	38 (4.8)
Injection site hemorrhage	17 (4.8)	31 (4.0)
Sinusitis	17 (4.8)	30 (3.8)
Back pain	16 (4.6)	29 (3.7)
Oropharyngeal pain	16 (4.6)	29 (3.7)
Hypoglycemia	5 (1.4)	28 (3.6)
Upper respiratory tract infection	26 (7.4)	27 (3.4)
Injection site rash	0	19 (2.4)
Injection site edema	0	18 (2.3)
Urinary tract infection	9 (2.6)	9 (1.1)

Source: ISS, Table 6

Common adverse events were not summarized in the BLA submission for (1) the Amgen obesity trials not included in the ISS, (2) the Amylin obesity trials from the metreleptin-pramlintide development program, (3) the investigator-initiated metreleptin trials, nor (4) compassionate-use programs. The study report for the completed Amylin Phase 2 trial evaluating metreleptin + pramlintide indicates that injection site reactions were the most common adverse events in the metreleptin-only (5 mg) arm.

7.4.2 Laboratory Findings

Changes in ALT and AST, and BUN, serum creatinine, and 24h urine protein are discussed in the relevant subsections of Section 7.3.5, Submission Specific Primary Safety Concerns (Liver Findings and Nephropathy, respectively).

The only other mean change in safety laboratory parameters of note was a moderate decrease from baseline in alkaline phosphatase seen in the NIH trials. Alkaline phosphatase (total and bone-specific) have been shown to be positively correlated with measures of insulin resistance;[36] therefore the decrease may be consistent with the overall improvement in insulin sensitivity in this trial.

7.4.3 Vital Signs

Blood pressure and heart rate changes are reported in Section 7.3.5, Submission Specific Primary Safety Concerns (Cardiovascular-Related Adverse Events).

7.4.4 Electrocardiograms

A thorough QT/QTc study was not conducted in this development program. Electrocardiograms (ECGs) were collected in the metreleptin-pramlintide for obesity development program. In the DFA102 trial, which examined the effect on body weight of various doses of metreleptin and pramlintide administered alone or in combination, there were no clinically significant changes or trends from enrollment in ECG tracings, including QT/QTc interval, in any treatment group during the trial.

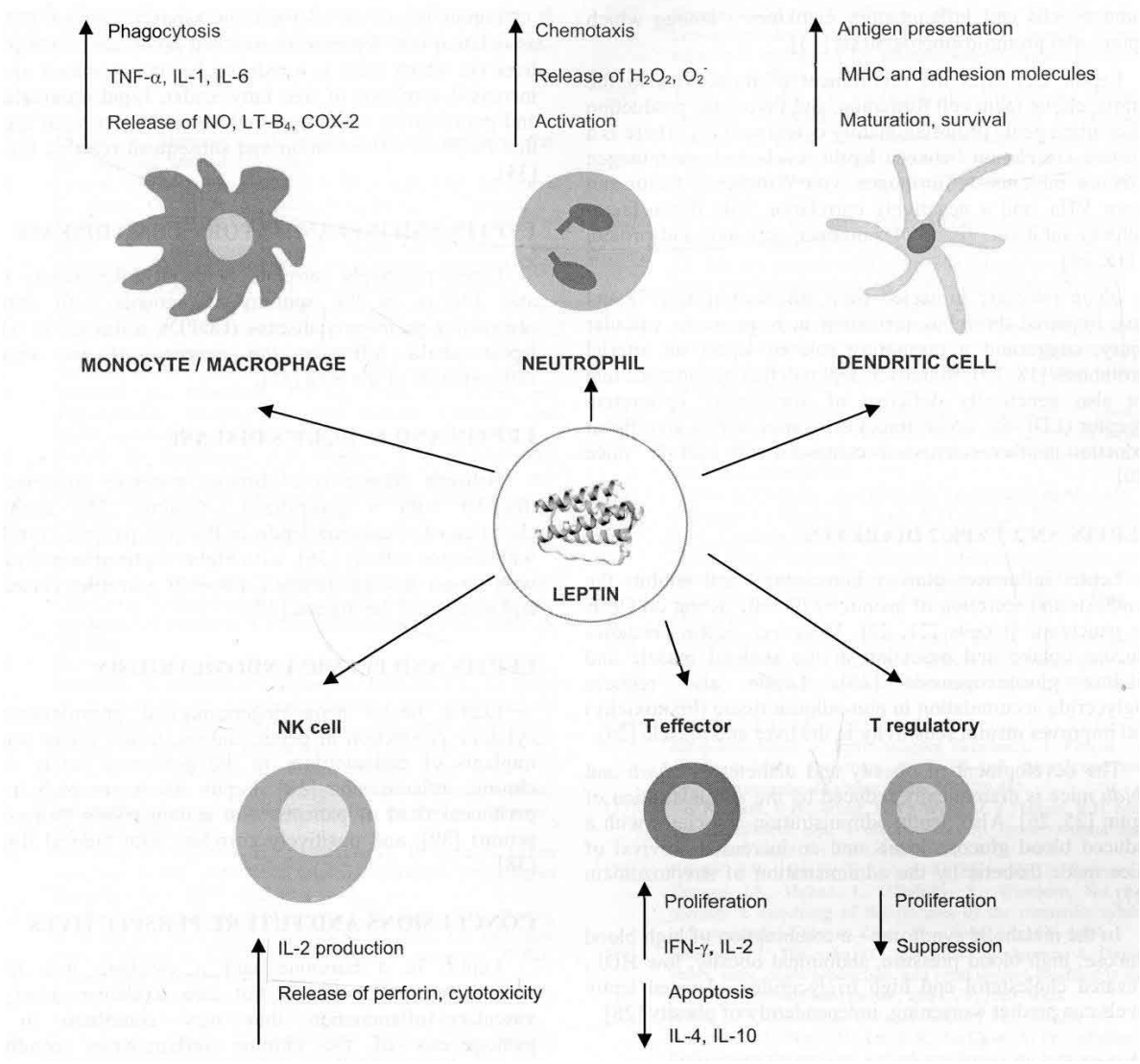
7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

The potential for immunogenicity with metreleptin is high. This is due to drug product-related factors, such as aggregate formation, non-physiological pH, route of administration (subcutaneous), and dosing frequency (daily). In addition, other factors, such as leptin's role in inflammation, as well as patient-related factors may contribute to its immunogenic potential. Leptin activates a number of cell signaling pathways important in T-cell activity and as shown in the figure below, leptin is permissive in cellular proliferation and cytokine production.

Figure 27. Schematic Representation of Leptin Proinflammatory Activities on Immune Cell Subsets



Source: Reference 37

Binding Antibodies

Almost all patients treated with metreleptin develop binding antibodies. In the NIH trials, 86% of patients, FHA101 trial 96% of patients, in the five trials in the Amgen obesity ISS 85% of patients (using a different assay), and in the Amylin obesity (pramlintide-metreleptin) program, 96-100% of patients developed binding antibodies to metreleptin. Development of antibodies appears to result in increased total leptin concentrations to supraphysiologic levels (e.g., greater than 100 ng/mL, and in some cases up to 1000 ng/mL), likely due to delayed clearance of metreleptin bound to antibody and/or assay

interference. The most frequent adverse event associated with development of antibodies to metreleptin / increased antibody titer was inflammatory injection site adverse events.

Reviewer comment: In assessing adverse events that might be associated with development of antibodies, note that almost all patients exposed to metreleptin develop antibodies, and in addition, injection site reactions are a common adverse event associated with metreleptin use. Therefore, the association would be expected.

NIH Trials

Forty-three patients from the 72-patient NIH trials had antibody data available at the time of the BLA submission. Of these, the majority were female (88%) and white (58%); 29 (67%) were pediatric patients (less than 18 years of age), of whom 13 patients were aged 12 years or younger (the youngest patient was 2 years old). Thirty (70%) patients had generalized lipodystrophy (22 congenital and eight acquired) and 13 (30%) patients had partial lipodystrophy (11 familial and two acquired). Mean baseline HbA1c, fasting glucose, and triglyceride concentrations were similarly elevated for the 43 patients with antibody data, as for the 72 patients overall. Mean (± SD) baseline fasting leptin concentration for the 43 patients was 2.1 ± 2.1 ng/mL, consistent with that observed for the 72 patients overall.

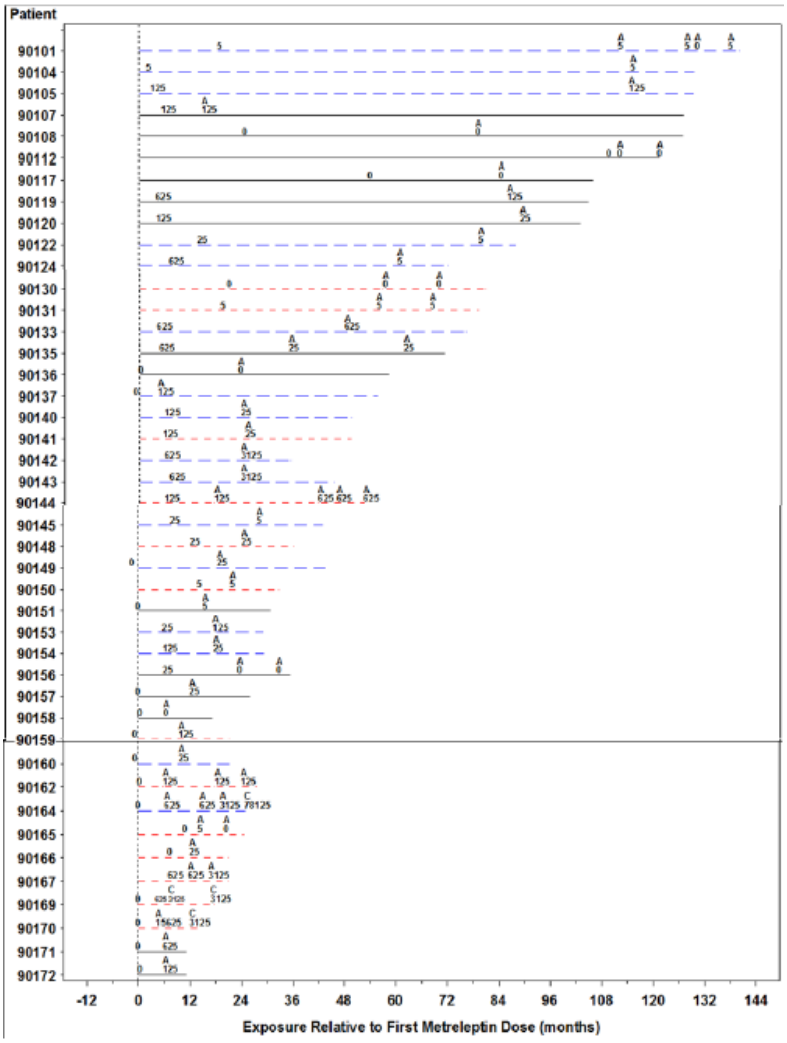
As noted by the sponsor, assessment of antibody status in the NIH trials was not performed in a systematic fashion. The sparse antibody assessments in combination with the varied exposure among patients provide suboptimal data, and results should be interpreted with caution. In patients with large intervals between antibody assessments, the peak (maximum) titer may not have been captured.

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 one month (Patient 90105) to 42 months (Patient 90144) following initiation of metreleptin for the time points at which samples were analyzed.

Most patients who developed binding antibodies to metreleptin continued to maintain an antibody titer on treatment. Antibody titer increased in seven patients (90142, 90143, 90144, 90153, 90164, 90167, and 90169). Other patients had stable or decreased antibody titer over time, despite continuing exposure to metreleptin. In one patient (90156) who initially developed an antibody titer, antibody was no longer observed despite continuing on metreleptin. Six patients (90108, 90112, 90117, 90130, 90136, and 90158) had no evidence of binding antibodies to metreleptin during treatment at the time points assessed. Exposure for these patients up to their last antibody measurement ranged from six months to 121 months. Seven patients (90149, 90151,

90157, 90159, 90160, 90171, and 90172) had only one post-baseline antibody assessment, and thus no determination could be made as to whether antibody titer was increasing or decreasing.

Figure 28. Titers of Binding Antibodies to Metreleptin and Neutralizing Activity Category†††††††††† During Metreleptin Treatment; NIH Trials (N = 43)



Horizontal line represents metreleptin treatment duration as of a data cutoff of 11 Jul 11.
Line styles indicate patient age group at enrollment: short dotted line for ≤ 12 years old, long dotted line for >12 and <18 years old, and solid line for ≥ 18 years old
Numbered data points indicate the titers of binding antibodies, where 0 indicates the absence of binding antibodies at the minimum dilution used and letter data points (A, B, C) indicate category of metreleptin neutralizing activity.
Source: Clinical Addendum, Figure 9

†††††††††† Note that the sponsor has categorized neutralizing activity with an *in vitro* assay from A to E, with A representing no neutralizing activity, and E representing the most potent. The classification is being used in this review for descriptive purposes. See the description in the neutralizing antibodies section, below.

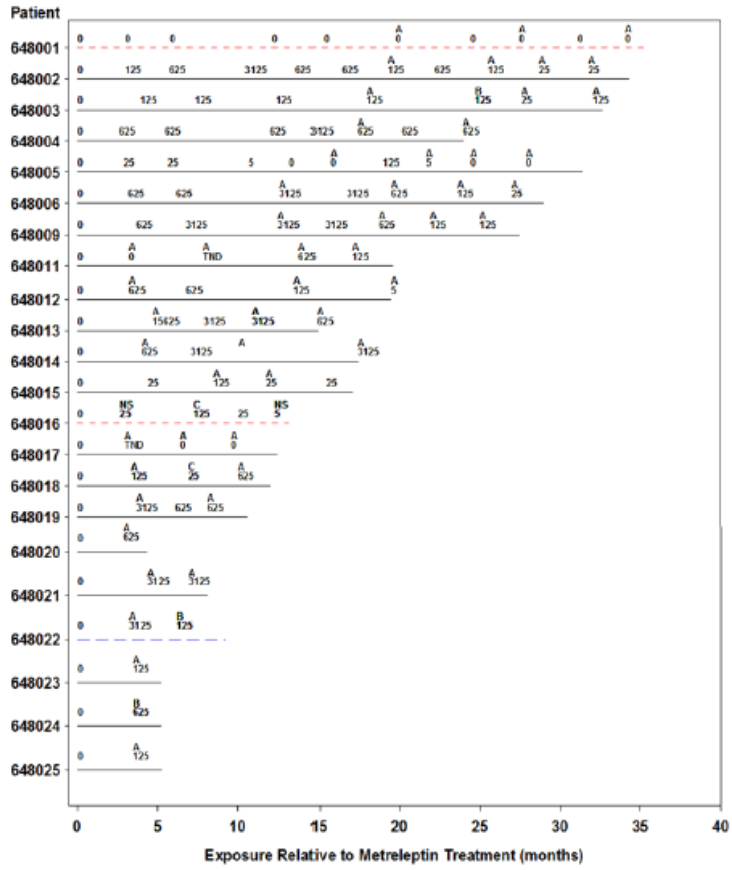
Trial FHA101

Of the 22 out of 28 patients with antibody data, the majority were female (91%) and white (73%); three were pediatric patients (less than 18 years of age), of whom two patients were aged 12 years or younger (the youngest patient was nine years old) at enrollment. Three (14%) patients were diagnosed with AGL and 19 (86%) patients were diagnosed with partial lipodystrophy (18 familial and one acquired). The majority of patients had HbA1c 6% or greater (n = 18, 82%), FPG 126 mg/dL or greater (14, 64%), or fasting TG 200 mg/dL or greater (15, 68%). Mean (±SD) fasting leptin concentration at baseline was 12.9 (± 10.7) ng/mL, with a maximum value of 42.9 ng/mL and with three patients (648001, 648016, and 648022) having leptin concentrations below the lower limit of quantification (less than 0.7 ng/mL).

Of the 22 patients with antibody data, 21 developed detectable binding antibodies following exposure to metreleptin, with titers ranging from 5 to 15625. One patient (648001, a 9-year-old female with AGL) had no evidence of antibodies to metreleptin over approximately 35 months of treatment. Of note, this patient had juvenile dermatomyositis treated with methotrexate; it is unknown if methotrexate treatment could have played a role in the lack of antibody response.

Of the 21 patients who developed binding antibodies to metreleptin, 15 patients continued to maintain an antibody titer on treatment, but the antibody titer tended to decrease over time in the majority of patients, despite continued exposure to metreleptin. In two patients (648005, 648017), antibody was no longer observed despite continued exposure to metreleptin. Four patients (648020, 648023, 648024, and 648025) had only one antibody assessment after baseline due to the timing of the data cut relative to initiation of metreleptin treatment.

Figure 29. Titers of Binding Antibodies to Metreleptin and Neutralizing Activity Category†††††††††† During Metreleptin Treatment; FHA101, N = 22



TND = titer not determined (but sample confirmed positive for binding antibodies); NS = non-specific.
Horizontal line represents metreleptin treatment duration as of a data cutoff of 07 Mar 2012.
Line styles indicate patient age group at enrollment: short dotted line for ≤ 12 years old, long dotted line for >12 and <18 years old, and solid line for ≥ 18 years old.
Numbered data points indicate the titers of binding antibodies, where 0 indicates the absence of binding antibodies at the minimum dilution used, and letter data points (A, B, C) indicate category of metreleptin neutralizing activity.

Neutralizing Antibodies

In both the NIH and FHA101 trials, all samples assessed for neutralizing activity were assayed in parallel to the binding antibody testing. Each test sample was categorized based on the potency and specificity of neutralizing activity. Potency was determined by successive dilution of samples for which test results were greater than the method-defined threshold inhibition value. Specificity was determined by assessing the effect of test sample addition on murine interleukin-3 (mIL-3)-dependent cell metabolism.

The following summarizes the categorization approach for neutralizing activity results with the sponsor's *in vitro* neutralizing activity assay:

- Category A: result is less than the assay cut-point on initial testing

- Category B: result is higher than the assay cut-point on initial testing, but is less than the assay cut-point on repeat testing

- Category C: result is higher than the assay cut-point on initial testing and re-testing, but is less than the assay cut-point after additional 1:10 dilution

- Category D: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 dilution but not after 1:100 dilution

- Category E: result is higher than the assay cut-point on initial testing and re-testing and after additional 1:10 dilution and 1:100 dilution

Patients Treated for Lipodystrophy

Three patients (90164, 90169, and 90170) from the NIH trials, all pediatric, have had neutralizing activity at the following time points: Patient 90164 at Years 2 and 3, Patient 90169 at Months 8 and 18, and Patient 90170 at Month 12. Two patients (648016 and 648018) from the FHA101 trial had neutralizing activity after approximately six months of treatment. One additional case from FHA101 was reported in the four-month safety update. This patient (648019), who had previously negative neutralizing assay (Category A) results, had a Category C result at a subsequent assessment at Month 18. Narratives for these six cases are presented below. All other patients tested from the NIH or FHA101 trials have had no evidence of neutralizing activity to date.

Patient 90164: At the time of the event, this was a 19-year-old female with CGL. This patient initiated therapy with metreleptin on 17 Mar 2010 at the age of 16. Her medical history included cirrhosis, hepatosplenomegaly, chronic gastritis, grade III esophageal varices, IgA nephropathy, proteinuria, diabetes with extreme insulin resistance, hypertriglyceridemia, hypertension, hirsutism, and amenorrhea. Concomitant medications at baseline included U-500 insulin and metformin. At baseline prior to initiation of metreleptin, plasma leptin concentration was 0.7 ng/mL, HbA1c was 9.8%, and serum TG was 600 mg/dL. See follow-up labs in the table below:

Table 76. Patient 90164: Available Antibody Status and Efficacy Labs Through Year 3

Date	Antibody titer	Neutralizing activity category	Leptin concentration (ng/mL)	HbA1c (%)	TG (mg/dL)
Mar 2010 (baseline)	NA	NA	0.7	9.8	600
Sep 2010	625	A	152.4	6.9	231
May 2011 (Yr 1)	625	A	318.3	6.7	168
Oct 2011	3125	A	NA	5.9	226
Apr 2012 (Yr 2)	78125	C	42.2	8.7	263
Aug 2013 (Yr 3)	NA	E	NA	7.4	674

The patient was hospitalized in (b) (6) for sepsis related to *Gemella* species (of note, hospital course was complicated by *Clostridium difficile* colitis) and again on (b) (6) (b) (6), for sepsis related to *Streptococcus viridans*, treated with a four-week course of IV ceftriaxone. She was unable to return to the NIH for her Year 3 scheduled visit in (b) (6) (b) (6) due to her hospitalization for sepsis. As a result, arrangements were made for a plasma sample to be collected by her local physician for antibody assessment. The sponsor was notified on 8 Aug 2013 that this plasma sample was tested for neutralizing activity category E (high potency activity). Binding antibody assessment is still pending at the time of this writing. No clinical laboratory tests were done at this visit. The patient is scheduled for a follow-up visit with her local physician on 20 Aug 2013. [Supplemental information received 26 Aug 2013 reported non-fasting lipids and laboratory results from 20 Aug 2013 which included: total cholesterol 269 mg/dL, HDL-cholesterol 25 mg/dL, non-HDL-C 244 mg/dL, cholesterol / HDL ratio 10.8, LDL-C 152 mg/dL, TG 674 mg/dL, HbA1c 7.4%.] As of 18 Sep 2013, the patient remained on metreleptin. In Oct 2013, an event of malignant otitis externa with *Stenotrophomonas maltophilia* bacteremia for which the patient was hospitalized in (b) (6) was reported. FDA received safety reports of two additional hosptializations for bacterial infections under the NIH trial IND. The patient was admitted on (b) (6) for fever (104.1°F). Blood cultures grew *S. viridans*. The patient was treated with IV nafcillin then switched to ceftriaxone for six weeks via peripherally inserted central catheter (PICC). Most recently, the patient was sent to the local hospital by her primary physician for positive blood cultures with *Acinetobacter baumanii* (collected (b) (6)). The patient had complained of feeling weak and sick and febrile for three days prior and experienced rigors the night before her hospital admission (temperature was 101°F). The patient was started on meropenem and the PICC line (still in place from the previous infection treatment) was removed. The patient also complained of abdominal pain, which was thought due to C. diff. colitis. The patient was discharged home (b) (6) on oral ciprofloxacin for acetinobacter bacteremia and oral vancomycin for C. diff.

Reviewer comment: This case is confounded by the patient's medical history that could compromise the immune system and predispose to infections (diabetes, cirrhosis) and complicated by repeated hospitalizations, catheters, and antibiotics. While some of the organisms could be oral flora, and poor dentition

was reported in the notes from the hospital, S. maltophilia can cause nosocomial infections in immunocompromised patients.[38] It is also notable that no source for her initial infections was found (e.g., no evidence for endocarditis on echocardiogram). Whether neutralizing antibodies to leptin could play a role in the development of the numerous bacterial infections is unknown. With respect to the potential for loss of efficacy, it is noted that HbA1c and TG increased after Year 1. A blood glucose value reported in the most recent post-hospitalization doctor's note (finishing 14-day course of levofloxacin, but not reported to be actively infected) was 354 (units not provided). She was also reported to have hepatomegaly at that visit; it is unknown if this had improved at some point initially on metreleptin.

Patient 90169: This was a 4-year-old female with CGL at study entry. Antibody titer was negative at baseline (pre-dose), 625 at Month 4 (neutralizing activity not assessed), and 3125 at Months 7 and 17 (both with positive neutralizing activity, category C). Plasma leptin concentration was 0.7 ng/mL at baseline and increased to 12.3, 17.5, and 27.0 ng/mL at Months 4, 7, and 17, respectively. HbA1c increased from 8.7% at baseline to 10.5%, 10.0%, and 9.2% at Months 4, 7, and 17, respectively. Serum TG concentrations remained relatively stable during treatment (370 mg/dL, 322 mg/dL, 377 mg/dL, and 325 mg/dL at baseline, Months 4, 7, and 17, respectively). No adverse events were reported for this patient. This patient appeared to be a non-responder to metreleptin treatment. Per the study investigators, compliance was an issue in this 4-year-old patient, and the assessment by the site was that the patient actually received only a small percentage of prescribed therapy during the initial seven months, after which compliance improved but may still have been below 70%. In the four-month safety update, results from Month 24 were reported: antibody titer was 625 and neutralizing activity was negative (Category A). Leptin concentration was 58.7 ng/mL. The patient's metabolic control improved, with HbA1c decreased from 9.2% to 6.5% and TG decreased from 325 mg/dL to 224 mg/dL.

Patient 90170: This was an 11-year-old female with AGL at study entry. Antibody titer was negative at baseline (pre-dose), 15625 at Month 4 with negative neutralizing activity (Category A), and 3125 at Month 12 with positive neutralizing activity (Category C). Plasma leptin concentration was 1.0 ng/mL at baseline and increased to 72.3 ng/mL and 81.3 ng/mL at Months 4 and 12, respectively. HbA1c was in the normal range at baseline (5.3%) and remained stable during treatment. Serum TG concentrations were 368 mg/dL at baseline, 113 mg/dL at Month 4, and 253 mg/dL at Month 12. One adverse event of peripheral edema was reported for this patient 345 days after initiation of metreleptin. After the data cutoffs used for this document, a serious adverse event of anaplastic large cell lymphoma was reported for this patient (see Section 7.6.1, Human Carcinogenicity). At the time of the serious adverse event for anaplastic large cell lymphoma, the sponsor assessed the binding titer and neutralizing activity (Month 24), and this was reported in the four-month safety update. The patient's binding titer and neutralizing activity remained 3125 and positive

(Category C), respectively. Leptin concentration (112.2 ng/mL) and glycemic control (HbA1c 4.9%) remained constant; and TG modestly increased to 363 mg/dL. The patient discontinued metreleptin treatment on 25 Dec 2012, a few weeks after diagnosis of the anaplastic large cell lymphoma, but later reinitiated metreleptin treatment (12 Feb 2013).

Patient 648016: This was an 11-year-old male with AGL at study entry, who initiated metreleptin based on inclusion criteria of hypertriglyceridemia as well as a history of diabetes, although glycemic control was good at the time of starting metreleptin treatment (HbA1c 5.5%). Other considerations for initiating metreleptin therapy in this patient were chronic active autoimmune hepatitis (with severely elevated liver function tests), and aggressive behavior related to difficult to control hyperphagia (information reportedly on file at Amylin). Maximum binding antibody titer was 125 with positive neutralizing activity (Category C) at Month 6. Titer decreased to 5 at Month 12 (non-specific result for neutralizing activity), and was 25 at Months 15, 21, and 24 without neutralizing activity (Category A). Fasting leptin concentration was less than 0.7 ng/mL at baseline, increased to 3.6 ng/mL at Month 6, and decreased to 1.7 ng/mL at Month 12. HbA1c was normal at baseline (5.5%) and through Month 24 (4.6%). TG values were: 354 mg/dL at baseline, then 42 mg/dL, 469 mg/dL, 30 mg/dL, 41, 63, 196, and 66 mg/dL at Months 3, 6, 12, 15, 18, 21, and 24, respectively. AST and ALT decreased from 208 IU/L and 419 IU/L at baseline, respectively, through Month 24.

Patient 648018: This was a 40-year-old female with APL at study entry. Binding antibody titer was 125 at Month 3, 25 at Month 7 (Category C neutralizing activity), 625 at Month 10 (Category A neutralizing activity), and 125 at Month 18 (Category A neutralizing activity). Leptin concentration increased from 8.4 ng/mL at baseline to 20.7 ng/mL at Month 3, 40.7 ng/mL at Month 7, and 68.6 ng/mL at Month 10. HbA1c was normal (5.7%) at baseline and remained stable through Month 18 (5.7%). TG at baseline was 1243 mg/dL, then 471 mg/dL, 1435 mg/dL, and 597 mg/dL at Months 10, 15, and 18, respectively.

Patient 648019: This was a 55-year-old female with FPL at study entry. Binding antibody titer was 3125 at Month 3 (Category A neutralizing activity), 625 at Months 6 and 9 (Category A neutralizing activity at Month 9), 3125 at Months 12 and 15 (Category A neutralizing activity at Month 15), and 625 at Month 18 (Category C neutralizing activity). Leptin concentration increased from 2.7 ng/mL at baseline to 116.6 ng/mL at Month 3, 17.5 ng/mL at Month 6, and 27.7 ng/mL at Month 9. HbA1c was normal (5.6%) at baseline and remained stable through Month 18 (5.7%). TG was 79 mg/dL at baseline, and 121, 114, 131, 150, and 120 mg/dL at Month 6, 9, 12, 15, and 18, respectively.

Patients Treated for Obesity

No patients in the Amgen obesity trials were known to have developed neutralizing antibodies.‡‡‡‡‡‡‡‡‡‡‡

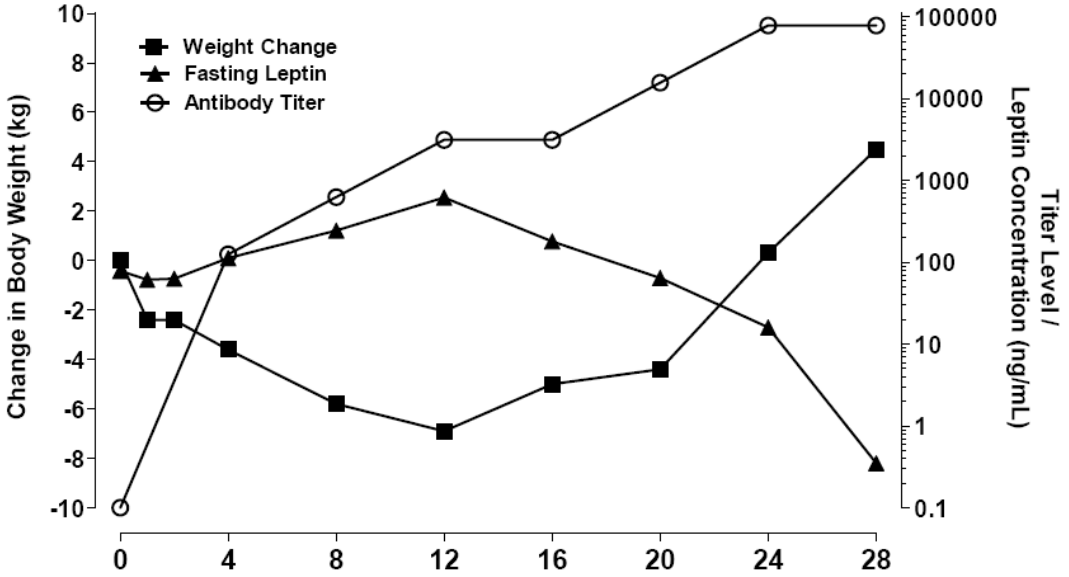
In the combined Phase 2 metreleptin-pramlintide trials, three patients out of 579 who were exposed to metreleptin have been identified with Category D or E antibodies, which indicate high potency neutralizing activity to metreleptin.

All three patients were enrolled in DFA102 and were characterized by: (a) high titer of binding-antibody to metreleptin; (b) plasma leptin concentration near or below the lower limit of the immunoassay sensitivity; and (c) weight regain following initial weight loss during the trial. On the basis of these findings, the first two identified patients were recalled to the study sites in November and December 2009 for additional clinical history and collection of samples for leptin and antibody assays. These tests suggested the presence of neutralizing activity against metreleptin in serum samples at the end of the 28-week study (present starting at ~20 to 24 weeks) as well as at the follow-up assessment (which occurred approximately 8 and 12 months after study termination).

- Patient 120011 was a 40-year-old white female randomized to metreleptin 5 mg (placebo + metreleptin). She had a baseline BMI of 42.5 kg/m^2 and a baseline body weight of 129.9 kg. During the trial, the patient experienced adverse events of injection site erythema, injection site pruritus, elevated ALT, injection site nodule, and injection site hemorrhage. Concomitant medications taken during the study included melatonin for insomnia, calamine lotion for injection site pruritus, and Zyrtec for injection site erythema and pruritus. At study termination on 25 Mar 2009, the patient weighed 134.4 kg, a gain of 4.5 kg from baseline. The patient did not enroll into the extension study (DFA102E). Approximately one month after study termination on 28 Apr 2009, the patient was seen by her PCP and weighed 145.5 kg (+15.6 kg from baseline). Over the next several months she continued to gain weight and developed impaired fasting glucose. On 23 Nov 2009, approximately eight months after study termination, the patient was brought back to the study site for follow-up evaluation of the clinical and laboratory findings described above of high binding-antibody titer, low plasma leptin level, and weight regain. At this visit, she weighed 155.9 kg (+26.0 kg from study baseline). Another follow-up visit with the patient was attempted but the patient did not respond to three attempts of contact by the study site. No further information on this patient is available.

‡‡‡‡‡‡‡‡‡‡‡ Note that the Amgen assay is different from the Amylin assay, and may be less sensitive.

Figure 30. Plasma Leptin Concentration, Metreleptin Binding-Antibody Titer, and Change in Body Weight over Time for Patient 120011 in DFA102

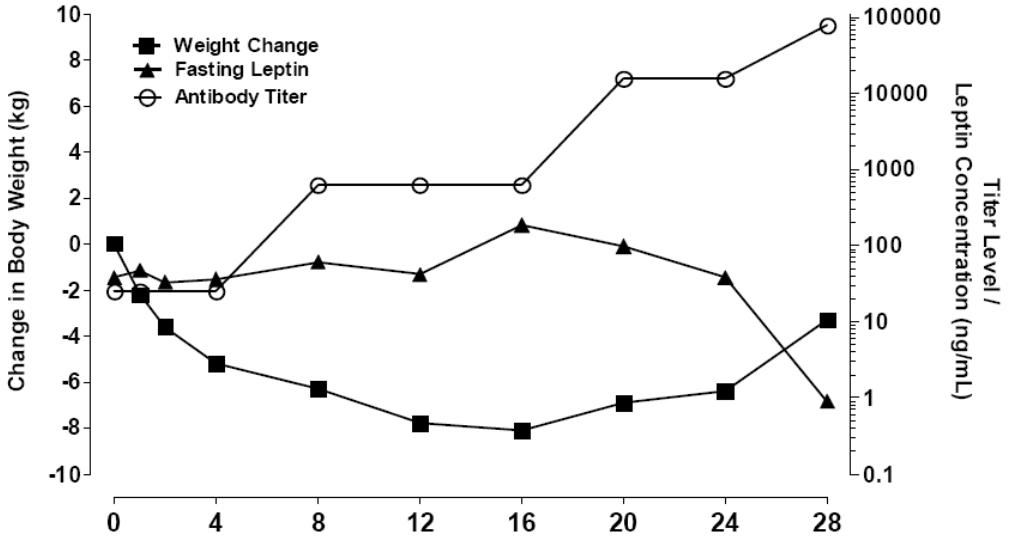


Source: IND 50259 15-day safety report

Reviewer comment: This figure does not reflect the 26 kg from baseline that the patient gained over eight months after study termination.

- Patient 130019 was a 48-year-old white male randomized to pramlintide 180 mcg + metreleptin 2.5 mg. The patient had a baseline BMI of 38.2 kg/m^2 and a baseline body weight of 127.9 kg. During the trial, the patient had an initial weight loss of 6.3% by Week 16 and ended the study with weight loss of 2.6%. At study termination binding antibody titer was maximal (78125) and coincided with low leptin concentrations. During the trial the patient experienced adverse events of diarrhea and stomach discomfort, injection site pruritus, nausea, and a sore throat. The patient did not enroll into the extension study. In April 2009, approximately four months after study termination the patient was diagnosed with type 2 diabetes. On 15 Dec 2009, approximately 12 months after study termination, the patient was brought back to the study site for follow-up evaluation of the clinical and laboratory findings of high binding-antibody titer, low plasma leptin level, and weight regain. At this visit, he weighed 140.5 kg (+12.6 kg from study baseline). On 15 Jan 2010, high antibody titer and low plasma leptin concentrations were again noted. On 07 Oct 2010 the patient did not return for a visit, but reported that his medical history was stable with no significant changes or events or new diagnoses since the last follow-up visit and his weight was 128.2 kg. (Of note, his baseline weight at the start of the DFA102 study was 128 kg; therefore, his self-reported weight appeared to return back to baseline.)

Figure 31. Plasma Leptin Concentration, Metreleptin Binding-Antibody Titer, and Change in Body Weight over Time for Patient 130019 in DFA102



Source: IND 50259 15-day safety report

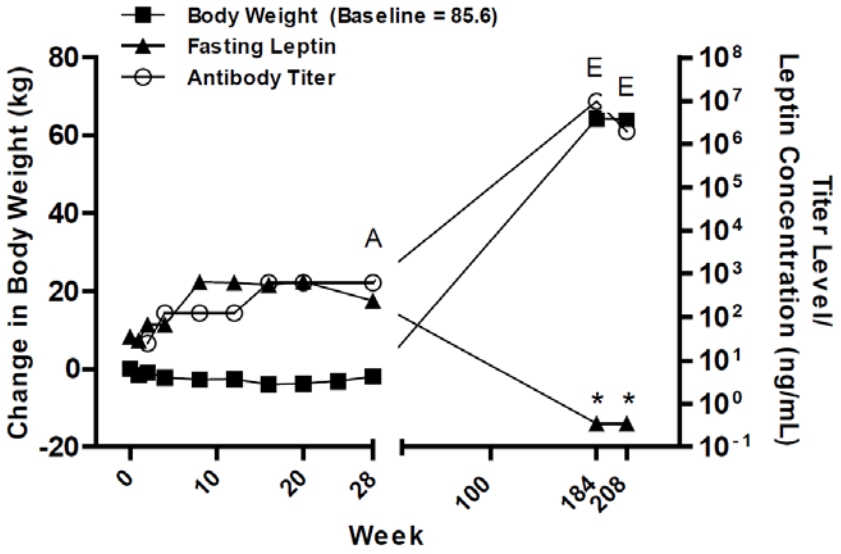
Reviewer comment: This figure does not reflect the 12.6 kg from baseline that the patient gained over 12 months after study termination.

Subsequent to these two submissions a third case of positive neutralizing activity to metreleptin was identified during the testing of plasma samples collected in DFA106. DFA106 was a safety follow-up study under IND 50259 (metreleptin for obesity) designed to acquire long-term follow-up from patients who received at least one dose of study medication during Amylin's obesity development program (trials DFA101, DFA102, and DFA102E). This study was conducted in response to the two patients in study DFA102 who were identified to have developed neutralizing activity to metreleptin and weight gain.

- Patient 139005 was a 39-year-old black female who was randomized to metreleptin 2.5 mg BID plus pramlintide 360 mcg BID in DFA102. Her baseline BMI was 33 kg/m^2 and weight was 85.6 kg. At study termination, her weight was 83.6 kg. The patient's last dose of trial medication was 28 Nov 2008. On Jan 13, 2012, at the follow-up visit for DFA106, additional relevant medical history included abnormal weight gain, shortness of breath, arthralgia, hypopituitarism, peripheral edema, back pain, hyperglycemia, and vitamin D deficiency. She had a plasma sample demonstrating very high anti-leptin binding antibody titer (9,765,625) and no detectable leptin (less than 0.7 ng/mL). The patient's weight on 14 Jan 2012 was 150.0 kg (i.e., weight gain of 66.4 kg since study termination). On 5 Apr 2012, approximately 1225 days after the last dose of study drug, neutralizing activity (category E) to metreleptin was detected in the patient's plasma sampled under

study DFA106. Follow-up weight reported from June 2013 (54 months after study termination) remained unchanged at 150 kg. Metreleptin antibodies titer was 1,953,125 and metreleptin neutralizing activity was category E.

Figure 32. Plasma Leptin Concentration, Metreleptin Binding-Antibody Titer, and Change in Body Weight over Time for Patient 139005 in DFA102 and DFA106



Source: IND 50259 15-day safety report

Potentially Immune-Related Adverse Events

Patients Treated for Lipodystrophy

Metreleptin could, in theory, exacerbate autoimmunity based on the role of leptin in regulating immune function. Autoimmune adverse events are highlighted in other sections of this review. The sponsor identified the following adverse events consistent with autoimmune disease in the NIH trials:

Table 77. Patients with Adverse Events Consistent with Autoimmune Disease, NIH Trials

Patient ID	Age (years) and Gender (M/F)	LD Subtype	Relevant Medical History	Relevant Adverse Events
90107	42 yr F	FPL	No relevant medical history	Lupus anticoagulant
90109	13 yr F	AGL	Type 1 diabetes mellitus	Chronic inflammatory hepatitis, Membranoproliferative glomerulonephritis
90110	8 yr F	AGL	Hashimoto's thyroiditis, Kawasaki's disease, Autoimmune hepatitis, Common variable immunodeficiency	Elevated ALT, Worsening autoimmune hepatitis, Parainfluenza pneumonia, streptococcal pharyngitis, URI, sinusitis, ear infection, flu
90113	12 yr F	CGL	No relevant medical history	Hashimoto's thyroiditis
90114	35 yr M	AGL	Chronic renal failure, Proteinuria	Membranoproliferative glomerulonephritis

Based on Sponsor review of TEAEs.
Source: Response to FDA Request for Information Dated 08-Oct-2013, Table 14

In the NIH trials, 11 (15.3%) of 72 patients experienced 13 events of potentially immune-related adverse events, including the events of urticaria (2.8%), anaphylactic reaction (1.4%), and papular rash (1.4%).

- Patient 90104 was a 17-year-old female with CGL at study entry who experienced pruritus 41 days after initiating metreleptin treatment. The event was treated with loratadine and resolved after 30 days. The patient was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90105 was a 14-year-old female at study entry with CGL who experienced urticaria (verbatim: hives) approximately 2.5 years after initiating metreleptin treatment. The patient discontinued use of metreleptin on her own from 01 Dec 2002 to 15 Mar 2003. The event of urticaria occurred 07 Mar 2003 while she was off metreleptin. She resumed metreleptin on 15 Mar 2003 until 07 Apr 2003. The event of urticaria was treated with cetirizine hydrochloride and hydroxyzine and resolved within a month. The patient was off metreleptin treatment again from 07 Apr 2003 until 29 Oct 2003 due to poor compliance but restarted metreleptin on 29 Oct 2003 and was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90109 was a 13-year-old female at study entry with AGL. The patient experienced papular rash (verbatim term: red, vesicular rash on face, 2-3 papules) approximately 14 months after initiating metreleptin treatment. The event resolved two days later. The patient was withdrawn from the study approximately one month after the event due to "health issues".

- Patient 90110 was an 8-year-old female at study entry with AGL who had a history of asthma and allergic rhinitis. The patient had an adverse event of asthma (verbatim term: asthma exacerbation) about six months after initiating metreleptin treatment and was treated with Seretide. A resolution date for the event was not provided. The patient continued study participation and was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90117 was a 45-year-old female with FPL who experienced an anaphylactic reaction to eating a moldy orange nearly four years after initiating metreleptin treatment. The patient presented to the emergency room with symptoms of hives, shortness of breath, upset stomach, diarrhea, and sore throat and was treated with IV benadryl and with Pepcid but was not hospitalized. The event was assessed by the investigator unrelated to metreleptin (rather, food-related) and resolved on the same day. The patient continued study participation and was still on metreleptin treatment as of the July 2011 data cutoff date.

- Patient 90135 was a 35-year-old female with FPL who experienced urticaria (verbatim: hives) about one month after initiating metreleptin treatment. The event was treated with IV Benadryl and resolved on the same day. The investigators noted that the urticaria was a precursor to the appendectomy that occurred on the same day. The patient continued study participation and was still on metreleptin treatment as of the July 2011 data cutoff date.

Other potentially immune-related but more non-specific events included arthralgia (four patients with one event each), and pruritus, asthma, eyelid edema, and injection-site urticaria (n = 1 for each event). The only adverse event considered related to metreleptin was the injection-site urticaria. None of these potentially immune-related events were considered serious or led to patient withdrawal from the study. All of these events were considered either mild or moderate in intensity except one event of asthma which was severe and occurred in a patient with a medical history of this condition.

In the FHA101 trial, nine (32.1%) of 28 patients experienced 13 events of potentially immune-related adverse events, including events of urticaria, swelling face, rash, pruritus, injection site inflammation, and injection site pruritus (all one patient for each event), and injection site urticaria (four patients with one event each). Further detail on the events of face swelling, urticaria, and rash is provided below.

- Patient 648001 was a 9-year-old female at study entry with AGL. The patient experienced face swelling and erythema approximately two months after initiating metreleptin treatment. The event was treated with clindamycin and resolved after four days. The patient continued study participation and was still on metreleptin treatment as of the March 2012 data cutoff date. The investigator assessment of this event was that it was questionable whether or not the patient had objective facial swelling. The event was not felt to represent a flare of her juvenile dermatomyositis.

The patient was felt to have an upper respiratory infection, and was treated for a possible sinusitis.

- Patient 648016 was an 11-year-old male at study entry with AGL who had a history of intermittent hives (starting about 4.5 years prior to starting metreleptin), which were treated with diphenhydramine. The patient experienced two events of urticaria. Onset of these events was 10 days and almost one year after the first dose of metreleptin. For the first urticaria event, the patient was treated with cetirizine, and the event resolved after 81 days. The metreleptin dose was briefly decreased. For the second urticaria event, the patient was treated with epinephrine, prednisone, ranitidine, and cetirizine, and the event resolved after five days. This patient also experienced rash approximately 3.5 months after initiating metreleptin treatment. The event was not treated and resolved after 19 days. The patient continued study participation and was still on metreleptin treatment as of the March 2012 data cutoff date.

- Patient 648019 was a 55-year-old female at study entry with FPL. The patient experienced pruritus 16 days after the first dose of metreleptin. This patient also had injection site urticaria in the same month as the event of pruritus (exact date not specified). The pruritus was treated with hydrocortisone cream. Both events were assessed by the investigator as related to metreleptin and considered resolved within 1-2 months. The patient continued study participation and was still on metreleptin treatment as of the March 2012 data cutoff date.

Three other patients (648004, 648006, and 648014) had events of injection site urticaria, all with onset 22 days after the first dose of metreleptin. No concomitant medication was given for these events except for Patient 648014 (treated with topical clobetasol). The events resolved after 34, 66, and 15 days, respectively. One patient (648021) had two events of injection site inflammation, the first 20 days after starting metreleptin (treated with Benadryl and topical hydrocortisone) and the second approximately four months after starting metreleptin (not treated). The events resolved after 81 and 15 days, respectively.

Patients Treated for Obesity

In the five obesity trials that comprise the ISS (Amgen) the most common adverse events for metreleptin and placebo patients were injection-site reaction (59.8% versus 44.7%). Severe injection site reactions were noted in seven metreleptin-treated patients versus one placebo-treated patient. In addition to the preferred term ‘injection site reaction’, injection-site adverse events occurring more frequently in metreleptin-treated compared to placebo-treated patients included injection site erythema (10.8% versus 0.6%), injection site inflammation (4.8% versus 0.6%), injection site edema (2.3% versus 0.0%), injection site pruritus (8.0% versus 1.7%), and injection site rash (2.4% versus 0.0%). Non-injection site reaction adverse events reported to be associated with

hypersensitivity were experienced by 14% of metreleptin-treated patients versus 8% of placebo-treated patients; potential eosinophilia-related adverse events (e.g., myalgia, thrombophlebitis) were experienced by 6% of metreleptin-treated patients and 4% of placebo-treated patients. The number of patients experiencing events of anaphylactic reaction, angioedema, potential hypersensitivity-related cutaneous reactions was similar between metreleptin- (6.1%) and placebo- (5.7%) treated patients. The most common such adverse event was rash for both groups (2.4% metreleptin versus 2.8% placebo). There were no cases of Steven-Johnson syndrome or toxic epidermal necrolysis reported in any treatment group.

In the Amgen trials not included in the ISS and the metreleptin + pramlintide for obesity clinical program, the majority of potentially immune-related adverse events were related to injection site reactions. Other adverse events (hypersensitivity, rash, eosinophilia, joint swelling, arthralgias, arthritis) were infrequent. One notable event was a serious adverse event of hypersensitivity in a patient treated with metreleptin in Amylin trial DFA104. See Section 7.3.2, Nonfatal Serious Adverse Events for the narrative.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Because of the small number of patients, the highly individualized dose titration implemented in the lipodystrophy trials, and changes in dosing frequency over time, a dose-response for adverse events could not be assessed. However, the ISS (five pooled Amgen obesity trials) provide some insight into safety findings by dose. In these trials, a total of 1072 obese patients with or without diabetes received metreleptin at doses of 10 mg QD or BID and 20 mg QD or placebo up to 42 weeks. In general, a clear dose-response was not seen for most adverse events. See the tables below for adverse events by dose for patients in the obesity trials with and without diabetes, by system organ class and preferred term, respectively.

Table 78. Incidence of Treatment-Emergent Adverse Events Summarized by System Organ Class, ISS

	Overweight/Obese			Overweight/Obese with T2DM		
	Pbo N=251	**ML 10 mg N=214**	**ML 20 mg N=374**	**Pbo N=100**	**ML 10 mg N=61**	**ML 20 mg N=135**
All Adverse Events	207 (82.5)	192 (89.7)	354 (94.7)	92 (92.0)	53 (86.9)	125 (92.6)
Blood and lymphatic system disorders	0	0	5 (1.3)	0	0	1 (0.7)
Cardiac disorders	1 (0.4)	3 (1.4)	6 (1.6)	0	2 (3.3)	3 (2.2)
Ear and labyrinth disorders	10 (4.0)	1 (0.5)	8 (2.1)	0	1 (1.6)	4 (3.0)
Endocrine disorders	0	0	3 (0.8)	1 (1.0)	0	0
Eye disorders	7 (2.8)	2 (0.9)	10 (2.7)	2 (2.0)	0	4 (3.0)
Gastrointestinal disorders	46 (18.3)	30 (14.0)	82 (21.9)	33 (33.0)	12 (19.7)	25 (18.5)
General disorders and administration site conditions	142 (56.6)	175 (81.8)	332 (88.8)	70 (70.0)	42 (68.9)	105 (77.8)
Hepatobiliary disorders	2 (0.8)	0	0	0	0	0
Immune system disorders	4 (1.6)	3 (1.4)	8 (2.1)	5 (5.0)	2 (3.3)	6 (4.4)
Infections and infestations	92 (36.7)	86 (40.2)	126 (33.7)	40 (40.0)	23 (37.7)	51 (37.8)
Injury, poisoning and procedural complications	28 (11.2)	19 (8.9)	42 (11.2)	12 (12.0)	6 (9.8)	13 (9.6)
Investigations	5 (2.0)	3 (1.4)	7 (1.9)	8 (8.0)	2 (3.3)	6 (4.4)
Metabolism and nutrition disorders	6 (2.4)	1 (0.5)	6 (1.6)	9 (9.0)	10 (16.4)	25 (18.5)
Musculoskeletal and connective tissue disorders	44 (17.5)	36 (16.8)	65 (17.4)	19 (19.0)	10 (16.4)	22 (16.3)
Neoplasms benign, malignant and unspecified	3 (1.2)	3 (1.4)	1 (0.3)	2 (2.0)	0	4 (3.0)
Nervous system disorders	52 (20.7)	49 (22.9)	86 (23.0)	18 (18.0)	14 (23.0)	40 (29.6)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.3)	0	0	0
Psychiatric disorders	10 (4.0)	12 (5.6)	25 (6.7)	11 (11.0)	4 (6.6)	8 (5.9)
Renal and urinary disorders	3 (1.2)	1 (0.5)	1 (0.3)	7 (7.0)	1 (1.6)	5 (3.7)
Reproductive system and breast disorders	13 (5.2)	6 (2.8)	22 (5.9)	6 (6.0)	3 (4.9)	4 (3.0)
Respiratory, thoracic and mediastinal disorders	36 (14.3)	17 (7.9)	56 (15.0)	10 (10.0)	8 (13.1)	15 (11.1)
Skin and subcutaneous tissue disorders	26 (10.4)	22 (10.3)	46 (12.3)	10 (10.0)	6 (9.8)	19 (14.1)
Surgical and medical procedures	4 (1.6)	1 90.5)	2 (0.5)	0	0	1 (0.7)
Vascular disorders	5 (2.0)	8 (3.7)	8 (2.1)	4 (4.0)	1 (1.6)	2 (1.5)

Source: ISS, Supporting Data Summary 5.1

Table 79. Frequent (Incidence 5% or Greater in Any Treatment) Adverse Events by Preferred Term, ISS

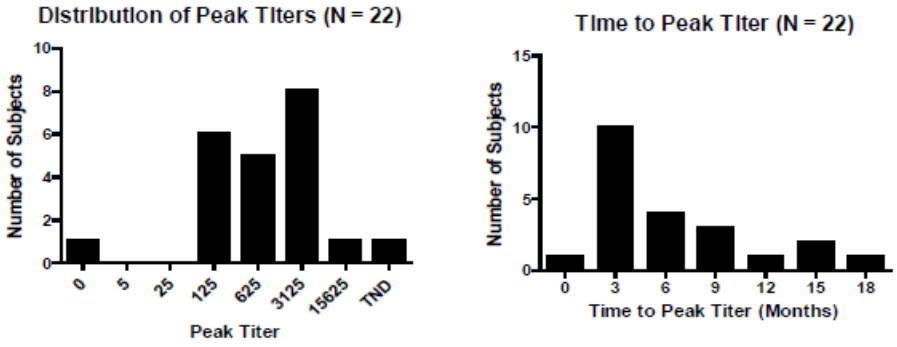
	Obese Subjects (N = 776) Studies 970164, 970213, 980236				Obese Subjects with Type 2 Diabetes (N = 296) Studies 970171 and 970188			
		Metreleptin				Metreleptin		
Preferred Term [2]	Placebo (N = 251) n (%)	10mg [1] (N = 214) n (%)	20mg [1] (N = 374) n (%)	All (N = 588) n (%)	Placebo (N = 100) n (%)	10mg [1] (N = 61) n (%)	20mg [1] (N = 135) n (%)	All (N = 196) n (%)
Any Treatment-Emergent Adverse Event	**207 (82.5)**	**192 (89.7)**	**354 (94.7)**	**546 (92.9)**	**92 (92.0)**	**53 (86.9)**	**125 (92.6)**	**178 (90.8)**
Back pain	14 (5.6)	11 (5.1)	14 (3.7)	25 (4.3)	2 (2.0)	1 (1.6)	3 (2.2)	4 (2.0)
Diarrhoea	11 (4.4)	3 (1.4)	27 (7.2)	30 (5.1)	6 (6.0)	4 (6.6)	8 (5.9)	12 (6.1)
Fatigue	15 (6.0)	8 (3.7)	28 (7.5)	36 (6.1)	9 (9.0)	3 (4.9)	11 (8.1)	14 (7.1)
Headache	33 (13.1)	33 (15.4)	63 (16.8)	96 (16.3)	10 (10.0)	7 (11.5)	20 (14.8)	27 (13.8)
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.0)	9 (14.8)	19 (14.1)	28 (14.3)
Influenza	19 (7.6)	19 (8.9)	22 (5.9)	41 (7.0)	5 (5.0)	1 (1.6)	6 (4.4)	7 (3.6)
Injection site erythema	1 (0.4)	60 (28.0)	25 (6.7)	85 (14.5)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site haemorrhage	15 (6.0)	14 (6.5)	13 (3.5)	27 (4.6)	2 (2.0)	2 (3.3)	2 (1.5)	4 (2.0)
Injection site inflammation	2 (0.8)	27 (12.6)	11 (2.9)	38 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site oedema	0 (0.0)	12 (5.6)	6 (1.6)	18 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pruritus	3 (1.2)	40 (18.7)	19 (5.1)	59 (10.0)	3 (3.0)	1 (1.6)	3 (2.2)	4 (2.0)
Injection site rash	0 (0.0)	11 (5.1)	8 (2.1)	19 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reaction	100 (39.8)	58 (27.1)	272 (72.7)	330 (56.1)	57 (57.0)	41 (67.2)	98 (72.6)	139 (70.9)
Nasopharyngitis	35 (13.9)	36 (16.8)	44 (11.8)	80 (13.6)	9 (9.0)	5 (8.2)	10 (7.4)	15 (7.7)
Nausea	8 (3.2)	10 (4.7)	25 (6.7)	35 (6.0)	9 (9.0)	1 (1.6)	6 (4.4)	7 (3.6)
Oropharyngeal pain	14 (5.6)	5 (2.3)	17 (4.5)	22 (3.7)	2 (2.0)	3 (4.9)	4 (3.0)	7 (3.6)
Sinusitis	12 (4.8)	4 (1.9)	16 (4.3)	20 (3.4)	5 (5.0)	2 (3.3)	8 (5.9)	10 (5.1)
Upper respiratory tract infection	14 (5.6)	1 (0.5)	7 (1.9)	8 (1.4)	12 (12.0)	5 (8.2)	14 (10.4)	19 (9.7)
Urinary tract infection	4 (1.6)	1 (0.5)	3 (0.8)	4 (0.7)	5 (5.0)	1 (1.6)	4 (3.0)	5 (2.6)

QD = once daily; BID = twice daily.
Notes: All 228 subjects in study 970213 received metreleptin during a 4-week induction period. Of these, 189 subjects were subsequently randomized, 126 to metreleptin and 63 to placebo. Hence, data for the 63 subjects randomized to placebo are included in the placebo (randomized treatment period) and metreleptin (induction period) columns as appropriate.
- Treatment-emergent adverse events were defined as any adverse event that began or worsened after subjects received the first dose of randomized study medication; for Study LEPT-970213, they were defined as any adverse event that began or worsened after subjects received the first dose of metreleptin during the 4-week metreleptin induction period for the 228 metreleptin-treated subjects; and any adverse event that began or worsened after subjects received the first dose of placebo during the 24-week treatment period for the 63 subjects randomized to placebo.
- Summaries by individual treatment are based on the treatment at or immediately prior to the onset of the adverse event.
- Subjects experiencing multiple episodes of a given adverse event are counted once in each relevant treatment.
[1] Doses indicated are per day; subjects received 10 mg per day (administered as 10 mg QD) or 20 mg per day (administered as 10 mg BID or 20 mg QD).
[2] Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 10.1 and upversioned to Version 13.0.
Source: ISS, Table 6

7.5.2 Time Dependency for Adverse Events

Time dependency of adverse events could not be formally assessed given the nature of the lipodystrophy data: because the trials are ongoing and since data are presented up to a number of data cuts, the amount of data varies across patients. Nevertheless, limited time-to-peak antibody data are available from a subset of patients from the FHA101 trial (note that some patients only have one post-treatment antibody assessment, and the sampling at intervals of approximately every three months may not be sufficiently frequent to capture the true peak titer).

Figure 33. Peak Titer Distribution and Time to Peak Titer of Antibodies to Metreleptin, FHA101 (N = 22)



7.5.3 Drug-Demographic Interactions

Subgroup analyses by sex and race were not conducted. The majority of patients in the NIH trials and FHA101 were female (83.3% and 92.9%, respectively) and white (61.1% and 75.0%, respectively). While male patients and Black, Asian, Native American, Hispanic, and other races were represented in the patient population, the number of patients was insufficient to examine the effect of either sex or race on adverse events.

See Section 7.6.3, Pediatrics and Assessment of Effects on Growth for a discussion of safety in the pediatric group.

7.5.4 Drug-Disease Interactions

Because lipodystrophy is a heterogenous disorder, certain co-morbidities are more common in certain types of lipodystrophy. For example, renal and liver disease may be more frequently associated with generalized versus partial lipodystrophy. In addition, some serious adverse events seemed to be clustered in the AGL group (e.g., lymphoma, possibly autoimmune diseases). Therefore, an exploratory analysis of adverse events by system organ class was conducted by diagnosis in the NIH trials. Differences between groups may reflect underlying diseases or differences in metreleptin response. Interpretation, however, is limited by the relatively small number of patients per group. Given the proportion of patients in the FHA101 trial with FPL (75%), adverse events presented only by generalized versus partial lipodystrophy are presented.

Table 80. Treatment-Emergent Adverse Events by Lipodystrophy Diagnosis and System Organ Class, NIH Trials

	CGL N=32	CGL%	AGL N=16	AGL%	FPL N=20	FPL%	APL N=4	APL%
Gastrointestinal disorders	12	37.5	4	25.0	7	35.0	3	75.0
Infections and infestations	11	34.4	5	31.3	6	30.0	2	50.0
Musculoskeletal and connective tissue disorders	8	25.0	3	18.8	3	15.0	2	50.0
Metabolism and nutrition disorders	4	12.5	6	37.5	4	20.0	1	25.0
Nervous system disorders	7	21.9	4	25.0	4	20.0	0	0.0
General disorders and administration site conditions	6	18.8	4	25.0	4	20.0	0	0.0
Skin and subcutaneous tissue disorders	5	15.6	2	12.5	6	30.0	1	25.0
Investigations	4	12.5	5	31.3	2	10.0	0	0.0
Renal and urinary disorders	5	15.6	2	12.5	4	20.0	0	0.0
Psychiatric disorders	3	9.4	5	31.3	1	5.0	0	0.0
Reproductive system and breast disorders	5	15.6	1	6.3	2	10.0	0	0.0
Blood and lymphatic system disorders	4	12.5	2	12.5	1	5.0	0	0.0
Respiratory, thoracic and mediastinal disorders	4	12.5	1	6.3	2	10.0	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	9.4	2	12.5	1	5.0	0	0.0
Vascular disorders	3	9.4	3	18.8	0	0.0	0	0.0
Cardiac disorders	2	6.3	2	12.5	0	0.0	0	0.0
Endocrine disorders	2	6.3	0	0.0	2	10.0	0	0.0
Eye disorders	0	0.0	1	6.3	3	15.0	0	0.0
Hepatobiliary disorders	0	0.0	3	18.8	1	5.0	0	0.0
Injury, poisoning and procedural complications	1	3.1	1	6.3	0	0.0	0	0.0
Immune system disorders	0	0.0	0	0.0	1	5.0	0	0.0
Surgical and medical procedures	0	0.0	0	0.0	1	5.0	0	0.0

Source: Reviewer generated from BLA 125390 datasets

Table 81. Treatment-Emergent Adverse Events by Generalized vs. Partial Lipodystrophy and System Organ Class, FHA101

	Generalized Lipodystrophy (N = 5)		Partial Lipodystrophy (N = 23)		All Patients (N = 28)	
System Organ Class	n (%) Events	EAER	n (%) Events	EAER	n (%) Events	EAER
All Adverse Events	**5 (100.0) 37**	**6.58**	**22 (95.7) 148**	**5.09**	**27 (96.4) 185**	**5.33**
Blood and lymphatic system disorders	1 (20.0) 1	0.18	3 (13.0) 5	0.17	4 (14.3) 6	0.17
Gastrointestinal disorders	4 (80.0) 14	2.49	12 (52.2) 25	0.86	16 (57.1) 39	1.12
General disorders and administration site conditions	2 (40.0) 2	0.36	11 (47.8) 18	0.62	13 (46.4) 20	0.58
Injury, poisoning and procedural complications	0 (0.0) 0	0.00	4 (17.4) 5	0.17	4 (14.3) 5	0.14
Metabolism and nutrition disorders	1 (20.0) 1	0.18	8 (34.8) 14	0.48	9 (32.1) 15	0.43
Musculoskeletal and connective tissue disorders	0 (0.0) 0	0.00	8 (34.8) 13	0.45	8 (28.6) 13	0.37
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (20.0) 1	0.18	0 (0.0) 0	0.00	1 (3.6) 1	0.03
Renal and urinary disorders	1 (20.0) 1	0.18	2 (8.7) 3	0.10	3 (10.7) 4	0.12
Reproductive system and breast disorders	1 (20.0) 1	0.18	2 (8.7) 2	0.07	3 (10.7) 3	0.09
Respiratory, thoracic and mediastinal disorders	1 (20.0) 1	0.18	3 (13.0) 3	0.10	4 (14.3) 4	0.12
Skin and subcutaneous tissue disorders	2 (40.0) 6	1.07	2 (8.7) 2	0.07	4 (14.3) 8	0.23

EAER = Exposure Adjusted Event Rate, calculated as dividing number of events by patient years of exposure as of data cutoff.
Notes: Treatment-emergent adverse events are defined as those that occurred during or after the first injection of metreleptin through the remainder of the study.
- n (%), where n represents number of patients experiencing at least one occurrence of a given event, %=100*n/N.

Source: Clinical Safety Update, Table 51

Adverse events were presented in the Amgen obesity five-study ISS by whether or not patients had a diagnosis of type 2 diabetes (since three trials evaluated a population of obese patients without type 2 diabetes and two trials were conducted in patients with obesity and type 2 diabetes). The only commonly-occurring adverse event identified that occurred in diabetes-only patients (and to a greater extent in metreleptin- versus placebo-treated patients), was hypoglycemia (see Section 7.3.5, Submission Specific Safety Concerns).

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction evaluations were conducted in the lipodystrophy population. The only interaction that was decribed in this population was a pharmacodynamic interaction (hypoglycemia) between metreleptin and anti-hyperglycemic medications.

In the NIH trials, hypoglycemia was reported in eight (11.1%) of 72 patients, and occurred only in patients also using insulin (with or without oral anti-hyperglycemic agents). The investigator felt that most hypoglycemia events were related to concomitant insulin and metreleptin use, likely resulting from inadequate reductions in insulin doses in the face of marked improvements in insulin sensitivity associated with metreleptin treatment. In FHA101, hypoglycemia was reported in seven (25.0%) of 28 patients. All patients who experienced hypoglycemia adverse events were receiving either concomitant insulin therapy or a sulfonylurea, with or without other oral anti-hyperglycemic agents, except for one patient who was on insulin until about 3 to 4

months before the event of hypoglycemia but was only on metformin at the time of the event.

Reviewer comment: While it is most likely that patients who develop hypoglycemia on metreleptin will be taking other anti-hyperglycemic medications, note that in the Amgen ISS, adverse events described by the preferred term 'hypoglycemic reaction' not only occurred in patients who were on anti-hyperglycemic medications, but also in patients with diabetes who were controlled with diet only (13% metreleptin, 6% placebo in the diet-only diabetes trial).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Background

Metreleptin is not genotoxic and no adverse hematological effects or bone marrow abnormalities were observed in the chronic mouse and dog toxicity studies.[39] The Division is aware, however, of an extensive literature that suggests a link between leptin and cancer (reviewed in 40, 41).

Upon learning of the third case of non-Hodgkin's lymphoma (NHL) in the lipodystrophy program in early 2013 (narratives are presented later in this section), our Division consulted experts from FDA's Division of Hematology Products (DHP) to evaluate these cases. Because hematological malignancies have been reported in the literature in patients with lipodystrophy not treated with metreleptin (see the table below; note that the cutaneous manifestations of the two cases of T-cell lymphomas presented concurrently with fat atrophy), we additionally asked about the expected prevalence of NHL in a population this size (N = 125, including data from the four-month safety update) and whether certain types of lipodystrophy could render a patient more susceptible to hematological malignancy.

Table 82. Reports of Hematological Malignancies in Patients Diagnosed With Lipodystrophy Who Were Not Being Treated With Leptin

Patient	Malignancy	Summary
Male / AGL	Peripheral T-cell lymphoma	Male patient with Down syndrome who developed cutaneous peripheral T-cell lymphoma with AGL[42]
Male / lipoatrophy and panniculitis	Peripheral T-cell lymphoma presenting as lipoatrophy	47-year-old man with lymphoma presenting as panniculitis developing into profound lipoatrophy[43]
Female / partial lipodystrophy and scleroderma	Hodgkin's lymphoma	22-year-old female with generalized lipodystrophy and scleroderma who developed Hodgkin's lymphoma. The authors note that Sjögren's syndrome has been associated with lipodystrophy, scleroderma, and malignant lymphoma and suggest the possibility that lipodystrophy and scleroderma may contribute to the development of Hodgkin's disease or malignant lymphoma.[44]
Female / partial lipodystrophy	Pre-B ALL	Patient with partial lipodystrophy, acanthosis nigricans, and insulin resistance who developed pre-B ALL[45]

Source: BMS Metreleptin PubMed Literature Search; submission 24 Jun 2013; Table 6

The median age at diagnosis for NHL is 66 years, and the incidence of NHL increases with increasing age. The incidence in males is 23.8 per 100,000 and the incidence in females is 16.3 per 100,000.[46] The incidence for NHL in patients with lipodystrophy treated with metreleptin in the BLA trials is 1 of 17 enrolled male patients or 5.9% and 2 of 108 female patients or 1.9%, which translates to 5900 per 100,000 in males (a 248-fold increase over the incidence in the general population) and 1900 per 100,000 in females (a 117-fold increase). In addition, all three NIH patients developed T-cell lymphoma, which is much rarer. The incidence of T-cell lymphoma in the U.S. for males is 2.3 per 100,000 and for females is 1.4 per 100,000;[46] the incidence of T-cell lymphoma in the trials is a 2565-fold increase and a 1357-fold increase for males and females, respectively. Note that because of the small population in the BLA clinical trials (N = 125, including the patients in the four-month safety update), these estimates have wide confidence intervals.

Whether the increased risk of NHL (or, more specifically, T-cell lymphoma) is related to the underlying condition (lipodystrophy) or the treatment (metreleptin) is unknown.

Immunodeficiency and autoimmunity are associated with an increased risk for NHL.[47,48,49,50] Despite the few isolated case reports of concurrent diagnoses of lipodystrophy and lymphoma (see table above), a case series of patients with lipodystrophy without metreleptin treatment to adequately evaluate the risk of development of lymphoma in patients with non-HIV lipodystrophy is not available. Furthermore, it is biologically plausible that metreleptin could impact susceptibility to NHL and other malignancies, as described below:[§§§§§§§§§§]

Leptin is a cytokine that uses the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway for signal induction. Leptin binding activates JAKs, which in turn phosphorylates cytokine receptors which allows selective binding of the STAT family.[51,52] Dysregulation of STAT proteins contributes to the pathogenesis of various types of lymphoid malignancies. Increased activity of STAT3 was reported in T-cell large granular lymphocytic leukemia.[53,54] Constitutive activation of STAT3 and STAT5 has also found to be an important event in the pathogenesis of anaplastic large cell lymphoma, T-cell angioimmunoblastic lymphoma, and Sezary syndrome.[51,55] Leptin exerts proliferative and antiapoptotic activities in a variety of cell types, including T lymphocytes, leukemia cells, and hematopoietic progenitors.[56] Leptin also affects cytokine production, the activation of monocytes/macrophages, wound healing, angiogenesis, and hematopoiesis. *In vivo*, leptin regulates inflammation, playing an inhibitory role on monocyte/ macrophage-mediated responses while exerting a permissive role on lymphocyte-mediated inflammation. Leptin either induces or increases cell proliferation of different cell types, including T lymphocytes, CD34+ cells, leukemia cells, and endothelial cells. Leptin also acts as an inhibitor of glucocorticoid-induced apoptosis in T lymphocytes and of apoptosis induced by cytokine withdrawal in leukemia cells.[57]

In addition to the specific question of lymphoma, the Division requested the sponsor conduct a literature search of leptin and cancer in general. The effects of leptin on cancer cell growth in *in vitro* and non-clinical studies are summarized in the following table:

[§§§§§§§§§§] Background provided by DHP Reviewer, Karen McGinn

Table 83. Effects of Leptin on Cancer Cell Growth Based on In Vitro and Non-Clinical Studies

Cancer Type	Effect on Cell Growth
Breast	• ↑ cell proliferation[58,59,60,61,62,63,64] • ↑ anchorage-independent growth[59] • ↑ ERK1/2, STAT3, Akt/GSK3, and PKCα pathways[58,59,60,61,62,63,64] • ↑AP1→↑cdk2, cyclinD1, pRb[59,61,63] • ↑AP1→↑aromatase[62] • →cMyc[64] • Modulates ER signaling[63] • ↑HER2 via EGFR and JAK[65,66] • Levels correlate with hTERT and BMI[67]
Colorectal	• ↑ cell invasion via PI3K→Rac and RhoA[68] • ↑cell growth via ↑ERK1/2[69,70] • PPAR-γ ligands ↑ ERK1/2 and compete[71,72,73] • NFκB→↓apoptosis[74]
Prostate	• ↑cell proliferation[75] • ↓apoptosis • ↑ERK1/2 in hormone resistance (HR)[76] • ↓cell growth in HR antagonized by insulin[77] • ↑JAK2/STAT3, p38 MAPK, and PKC→↑apoptosis[78] • In HR cells, ↑ AR →↓ apoptosis • ↑αvβ3 integrin via OBR1/IRS-1/PI3K/Akt/NF-κB →↓migration[79] • High leptin levels →↓proliferation & angiogenesis[80] • Leptin dose-dependent ↓ HR cell migration & invasion[81] • ↑proliferation via MAPK and PI3-K[76] • Leptin:adiponectin ratio affects proliferation via p53 and BCL-2[82]
Pancreatic	• ↓cell proliferation[83] • ↑STAT3 and STAT5b pathways[84] • ↓leptin & ↑adiponectin/leptin ratio in PC cells[85] • ↑MT1-MMP via KIF1B →↑ invasion[86] • Suppress SOCS3 →↑ leptin & STAT2 →↑ tumor development[87] • ↑JAK/STAT3 and STAT5b pathways[88,84]
Gastric	• ↑EGFR and JAK[89] • ↑STAT3 signal via OBR[87] • Time & dose-dependent ↓ proliferation via G0/G1 arrest[90] • ↑apoptosis via caspases 3 and 8[90]
Ovarian	• ↑ERK1/2 →↑cell proliferation[91] • Time- and dose-dependent ↑proliferation via ↓forkhead box O3 and p27, Bim[92] • ↑MEK/ERK1/2 and PI3K/Akt →↑cyclin D1, MCL-1 →↑proliferation and ↓ apoptosis[93,91] • ↑S and G2/M phases via ↑cyclins D & A, and ↓p21WAF1/CIP1 →↑proliferation[94] • ↓Bad, TNFR1, and caspase 6 →↓apoptosis[95] • ↑ERα signal via STAT3 →↑ proliferation
Lung	• ↑ERK1/2 →↑cell proliferation[96]
Leukemia and lymphoma	• LepRb and OBR mRNA detected in myeloid and leukemic lymphoid cell lines[97] • ↑cell proliferation in human myeloid leukemia cell lines and cell isolates from patients[98] • Additive or synergistic growth effects when combined with hematopoietic cytokines (e.g., IL-3, G-CSF, and SCF)[99] • ↑Bcl-2, cyclin D1 →↑cell cycle entry[100] • ↓ apoptosis → overall B-cell homeostasis

	• ↑PI3K/AKT → ↑ proliferation and ↓ apoptosis in DLBCL[101]
Thyroid	• ↑OBR expression in 80% of PTC tumors[102,103] • ↑XIAP (antiapoptotic protein) and PI3K/Akt → ↓ apoptosis & ↑ proliferation • ↑cell growth[104] • ↓ apoptosis • Modulates migration of cancer cells; ↓ follicular & anaplastic migration[105] • ↑MEK/ERK1/2 and PI3K/Akt →↑papillary migration
Hepatic	• Controversial role; promote HCC development or tumor growth inhibition[106,107] • Promotes fibrosis, angiogenesis • ↑TGFβ, type-I procollagen and tissue inhibitor of metallo-proteinase-1 via OBR[108,109] • ↑VEGF via HIF1a[109] • Leptin associated with NAFLD and NASH, which contribute to fibrosis and HCC[110] • In leptin deficiency, ↑NF-κB/p65, proinflammatory cytokines, proliferating cell nuclear antigen, and cell survival signals[111]
Skin/Melanoma	• ↑NO and circulating EPCs →↑vasculogenesis[112]

Abbreviations: Akt, Protein kinase B; AP1, activator protein 1; AR, androgen receptor; Bad, Bcl-2-associated death promoter; BCL-2, B-cell lymphoma 2; BMI- body mass index; cdk, Cyclin -dependent kinase; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; EPC, endothelial progenitor cell; ER, estrogen receptor; ERK, extracellular signal regulated kinases; G-CSF, Granulocyte colony-stimulating factor; GSK, Glycogen Synthase Kinase; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HIF1a, hypoxia inducible factor 1; HR, Hormone resistant; hTERT, human telomerase reverse transcriptase; IL-3, interleukin 3; IRS, Insulin receptor substrate; JAK, Janus kinase; KIF1B, kinesin family member 1B; MAPK, mitogen-activated protein kinases; MCL, Induced myeloid leukemia cell differentiation; MEK, mitogen-activated protein kinase (MAPK) kinase; MT1-MMP, Matrix metalloproteinase; NAFLD, nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; NFκB, Nuclear Factor-Kappa B; OBR1, long form of the leptin receptor; NO, nitric oxide; OBR, leptin receptor; p21WAF1/CIP1, cyclin-dependent kinase inhibitor 1; PC, prostate cancer; PI3K, Phosphoinositide 3-kinase; PKC, Protein kinase C; PPAR, peroxisome proliferator-activated receptors; pRb, phosphorylated retinoblastoma protein; PTC, papillary thyroid cancer; Rho, Ras homolog; SCF, Skp, Cullin, F-box containing complex; SOCS3, suppressor of cytokine signaling 3; STAT, Signal Transducer and Activator of Transcription; TGF, Transforming growth factor; TNFR1, TNF receptor 1; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein

Source: BMS Metreleptin PubMed Literature Search; submission 24 Jun 2013; Table 4

Reviewer comment: While there are some conflicting data from the* in vitro *studies, on balance it appears that leptin signaling promotes cell growth and survival and inhibition of apoptosis. These findings support plausible mechanisms whereby metreleptin may promote tumor growth in a susceptible patient.

Observational data suggest that elevated leptin concentrations and leptin/leptin receptor tissue expression may be associated with certain cancers in humans. The long form leptin receptor (Ob-Rb) is present in hypothalamic regions implicated in the regulation of feeding behavior and energy balance, whereas the short leptin receptor isoforms are expressed in choroid plexus, vascular endothelium, and peripheral tissues, such as kidney, liver, lung, and gonads.[5] High leptin receptor expression has been found in pancreatic insulinoma,[40] and also in tumors and sera of patients with endometrial cancer,[113] thyroid cancer,[114] and in some studies of leukemia/lymphoma.[115]

Leptin serum concentration was associated in some,[63,116] but not all,[117] publications of breast cancer, colorectal cancer (men only),[63] and one study of chronic lymphocytic leukemia with increased risk factors for cancer;[115] leptin concentrations were higher with

advanced cancer stage in some but not all studies. Leptin tissue expression was present in some reports of prostate cancer,[63] endometrial cancer, [118] and thyroid cancer.[114]

Cancer in the Metreleptin Clinical Trials

The sponsor summarized the individual patient data for malignancies in patients treated in metreleptin clinical trials and compassionate use programs; the summary table is below and discussion of individual cases follows. In summary, there were:

- Hematological malignancies: three cases of T-cell lymphoma, all in patients with AGL, and one case of lymphocytic leukemia in a patient with obesity (case described in Section 7.3.1, Deaths)

- Papillary thyroid cancer: one case in patient with CGL, and two********** cases in patients with obesity

- Breast cancer: One case in a patient with FPL, one case (*in situ*) not reported in the table below in a patient with AGL (see patient 90147, T-cell lymphoma), and two cases in patients with obesity
    - In addition, one case of breast cancer was reported in a patient with obesity treated with placebo

- Skin cancer: Two cases of malignant melanoma and two cases of basal cell carcinoma, all in patients with obesity, and one case of squamous cell carcinoma of the tongue in a patient with lipodystrophy associated with HIV.
    - In addition, two cases of basal cell carcinoma were reported in patients with obesity treated with placebo

- Others: One case of metastatic adenocarcinoma (AGL), one case of bile duct cancer (lipodystrophy patient in Japan), and one case of vaginal carcinoma in a patient treated with Fc-leptin (Amgen program)
    - In addition, one case of cervix carcinoma and one case of lung cancer were reported in patients treated with placebo

********** There was a fourth case of a patient treated with 12 doses of metreleptin who was diagnosed with papillary thyroid cancer one year after study discontinuation. This case was included in the table below, but given the short treatment duration and long duration off metreleptin, was not included in my count.

Table 84. Individual Patient Data for Malignancies

Cases Involving Administration of Metreleptin								
Indication for metreleptin therapy	**Document(s) Where Event Reported**	**Malignancy (PT)**	**Report Verbatim**	**Patient Demo**	**Relevant Medical History/Family History**	**Time to onset (Days)**	**Outcome**	**Other relevant information**
LD	BLA, Clinical Safety Update	T-cell lymphoma	T-cell cutaneous lymphoma	68 yr, M	Acquired generalized LD hypercellular marrow, leucopenia, pancytopenia, anemia, lymphadenopathy, enlarged spleen, hepatic cysts, hepatomegaly	249	Fatal (~6 months after discontinuing metreleptin treatment)	Skin nodule was noted and skin biopsy result compatible with peripheral T-cell lymphoma.
LD	BLA, Clinical Safety Update	T-cell lymphoma	T-cell lymphoma	59 yr, F	Acquired generalized LD (1999), severe intermittent neutropenia (Dec 2007), benign breast fibroma, lipoatrophic diabetes, non alcoholic steatohepatitis, goiter (multinodular), thyroidectomy, hepatosplenomegaly	210-240	Fatal (~7 months after discontinuing metreleptin treatment)	Neutropenia returned Jan-2008. Bone marrow biopsy revealed hypercellular bone marrow with marked atypical T-cell lymphocytosis and myeloid maturation with left shift. On an unspecified date subject developed skin nodules. Skin biopsy performed Jan-2009 revealed subcutaneous T-cell lymphoma, stage IV-A. Chemotherapy initiated.
LD	BLA, Clinical Safety Update	T-cell lymphoma	Anaplastic large cell lymphoma	13 yr, F	Acquired generalized LD, hyperinsulinism, severe insulin resistance, nonalcoholic steatohepatitis, hypertriglyceridemia, hypertension, advanced bone age	661	Not Resolved	Subject noted bump under Right breast (Dec2012). Ultrasound consistent with enlarged lymph node. Biopsy of mass performed and pathology results showed "anaplastic large cell lymphoma, ALK positive'. Leptin therapy was stopped on 25Dec12 and reinitiated on 12Feb13.
Obesity	BLA, Amgen 5-study ISS and in Clinical Safety Update discussion	Lymphocytic leukemia	Lymphocytic leukemia	67 yr, F	Obesity	28	Fatal	Patient was hospitalized with pneumonia 28 days after initiate study drug, lab test showed neutrophils 2%, lymphocytes 95%. A diagnosis of lymphocytic leukemia was made, treated with IV antibiotics and chemotherapy. Patient expired 2 months later.

Cases Involving Administration of Metreleptin (continued)								
Indication for metreleptin therapy	**Document(s) Where Event Reported**	**Malignancy (PT)**	**Report Verbatim**	**Patient Demo**	**Relevant Medical History/Family History**	**Time to onset (Days)**	**Outcome**	**Other relevant information**
LD	BLA, Clinical Safaety Update	Papillary thyroid cancer	Metastatic Papillary Thyroid Carcinoma	24 yr, F	Congenital generalized LD, Hashimoto's thyroiditis, lipoatrophic diabetes, insulin resistance Hypertriglyceridemia, pancreatitis	705	Recovered/Resolved (thyroidectomy)	Diagnosed with multiple thyroid nodules summer 2009; Pathology (APR2011): Metastatic papillary thyroid carcinoma involving 1 lymph node; multifocal papillary cancer, involving right isthums/pyramidal & left lobes; Hashimoto's chronic thyroiditis.
Obesity	BLA, DFA102 CSR, and assessment provided to FDA on 17 January 2011	Papillary thyroid carcinoma	Papillary thyroid carcinoma	51 yr, F	Obesity, thyroid mass, Seasonal allergic rhinitis, drug allergy (Sulfa drugs)	45	Resolved (thyroidectomy)	Thyroid mass diagnosed in Jul 2008, prior to initiation of study drug. Histopathology revealed papillary thyroid carcinoma.
Obesity	BLA, DFA102 CSR, and assessment provided to FDA on 17 January 2011	Papillary thyroid carcinoma	Papillary thyroid carcinoma	61 yr, F	Obesity, Enlarged thyroid (1981), a family of thyroid cancer (2 sisters)	166	Resolved (thyroidectomy)	Thyroid pathology report (Jun2009): Papillary carcinoma (1.0) limited to thyroid. Nodular hyperplasia and chronic thyroiditis. No lymphatic /capillary invasion or extrathyroid extension was noted
Obesity	Reported via investigator IND and included in the submission	Thyroid cancer	Thyroid cancer	22 yr, F	Obesity, thyroglossal duct cyst	515	Not Resolved	Approximately 1 year post completion of study, diagnosed with papillary thyroid cancer. No additional information. PK study with only ~12 doses administered over several weeks
Obesity	In DFA103 study CSR, submitted 20 June 2013	Invasive ductal breast carcinoma	Invasive ductal carcinoma, right breast	58 yr, F,	Obesity, pre-existing skin bump at the right axillary area (05/2010)	17	Unknown	Pre-existing skin bump at the right axillary area (05/2010), diagnosed as 'inflamed sweat gland'). Pathology report (10Feb2011) revealed that right axillary lymph node was positive for invasive mammary carcinoma

Cases Involving Administration of Metreleptin (continued)

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
LD	Reported via investigator IND and included in the submission	Breast cancer	Breast cancer	50 yr, F	Familial partial liposystrophy, hypertriglyceridemia, hepatic steatosis, myocardial infarction.	2903	Not reported	Diagnosed with stage 1 breast cancer after suspicious mammogram led to needle biopsy (29Apr2013). Outpatient mastectomy performed on 13May2013. Self reported by the patient, no medical records obtained yet.
Obesity	In BLA, Amgen 5-ISS	Breast cancer	Inflamed breast cancer (malignant)	51 yr, F	Obesity, Removal of benign lipoma Right breast (1980); hysterectomy (1987); hormone replacement treatment (since 1996, estrogen patch), hypothyroidism	324	Not reported	Patient had right breast discomfort in 1999; Biopsy right breast (19May1999) revealed inflammatory carcinoma of the skin and infiltrating ductal carcinoma. 05Aug1999 mammogram review of films from 1993-1995; 1995 films showed increased density in the area of the breast; subsequently diagnosed breast cancer. Investigator reported in summary: "It is possible that the film of 1995, which was taken before study, represents an abnormality that may have progressed to breast cancer."
Obesity	BLA, DFA102E CSR,	Malignant melanoma	Melanoma L Shoulder	51 yr, F	Obesity	100	Resolved	Non serious event noted on CRF. No further information.
Obesity	BLA, 5-study, Amgen 5-ISS	Malignant melanoma	5-6 cm firm lymph node 1 axilla (malignant melanoma)	68 yr, M	Lip and/or oral cavity cancer (1993); chest melanoma (1997), both surgically removed. Obesity, diabetes, hypertriglyceridemia, smoker (11 years)	150	Not reported	On 21Nov1998 physical exam found 5-6 CM firm lymph node on left axilla; biopsy performed (05Jan1999) revealed malignant melanoma; MRI revealed a 2-3 cm lesion in the left temporal lobe later with diagnosis 'brain metastasis with edema'.
Obesity	BLA, 5-study, Amgen 5-ISS	Basal cell carcinoma	Base cell cancer on (R) ear and nose	68 yr, M	Hodgkin's lymphoma (1957), smoker (12 years), hypercholesterolemia	480	Resolved (surgical removal of lesion)	Skin lesions on ear and nose were found during clinical study visit. Biopsy of right side of nose where glasses rest revealed basal cell carcinoma
Obesity	BLA, DFA102 CSR	Basal cell carcinoma	Basal cell carcinoma on face	57 yr, F	Obesity, hypercholesterolemia, allergy	129	Resolved	Non serious event noted on CRF, no further information.

Cases Involving Administration of Metreleptin (continued)

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
LD	BLA, Clinical Safety Update	Worsening of metastatic adenocarcinoma	adenocarcinoma, worsening	67 yr, F	AGL, known history of metastatic adenocarcinoma	78	Fatal	Subject had progressive adenocarcinoma of undetermined origin, complicated by a small bowel obstruction and apparent sepsis
HIV- related LD	Reported via investigator IND and included in the submission	Squamous cell carcinoma of the tongue	Squamous cell carcinoma of the tongue	49 yr, M	LD, hypertriglyceridemia, AIDS, Tongue lesion present prior to study initiation. 20 pack a year history of smoking.	64	Unknown	Developed tongue lesion after tongue cut on jagged crown, increasing in size in May 2006 prior to initiating Leptin vs. placebo. Biopsy of epiglottis (1988); no results. Pathology (date unknown) left lateral tongue lesion revealed squamous cell carcinoma.
LD	Reported in JNDA (KUTR-003-0)	Bile duct cancer	Hepatic mass	35 yr, F	Hypertension, hypertriglyceridaemia, hyperuricaemia, hepatic steatosis, diabetes mellitus diabetic neuropathy, diabetic retinopathy, pancytopenia,asteatotic leg dermatitis, amenorrhoea	791	Fatal	Sponsor requesting additional detail.

Cases Involving Administration of FC-leptin

Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
Obesity	Included in this submission as part of the Amgen studies outside the Amgen 5-study ISS	Vaginal cancer	Vaginal cancer	36 yr, F	History of abnormal pap smear (Sep 1999) with repeat also abnormal (Apr 2000). obesity	20	Not Resolved	Culposcopy 12May2000 initially inconclusive, final result (31May2000) revealed vaginal cancer. Subject withdrew from study on 26May2000 to undergo radiation treatment. No additional information.

Cases Involving Administration of Placebo								
Indication for metreleptin therapy	Document(s) Where Event Reported	Malignancy (PT)	Report Verbatim	Patient Demo	Relevant Medical History/Family History	Time to onset (Days)	Outcome	Other relevant information
Obesity	BLA, Amgen 5-study ISS	Cervix carcinoma	Cervix carcinoma	48 yr, F	Abnormal pap smear 22Dec1998, on birth control pills, Obesity	81	Unknown	Repeat pap smear (22-Mar-1999) abnormal; cervical biopsy (27-Mar-1999) revealed adenocarcinoma in situ; subject early termed from study due to family emergency.
Obesity	BLA, DFA104 CSR	Lung adenocarcinoma	Lymphangitic adenocarcinoma of the lung	60 yr, F	Obesity, persistent cough (Dec2010)	36	Fatal	Patient had history of persistent cough since Dec2010, prior to study enrollment. Apr-2011: Pathology from bronchoscopy: Adenocarcinoma of right lung bronchial washings. Pleural fluid positive for malignancy.
Obesity	BLA, DFA102 CSR	Basal cell carcinoma	Basal cell carcinoma on tip of nose	40 yr, F	Obesity	164	Resolved	Non serious event reported on CRF, no further information.
Obesity	BLA, DFA104 CSR	Basal cell carcinoma	left shoulder basal cell carcinoma	20 yr, F	Obesity	36	Resolved	Non serious event reported on CRF, no further information.
Obesity	BLA, Amgen, 5-study ISS	Breast cancer stage III	Adenocarcinoma - stage 3 - right breast	49 yr, F	Obesity, Lymphedema, On estrogen since 1995, obesity	300	Unknown	Fine needle and core biopsy on 21-Jan-2000 revealed Stage 3 adenocarcinoma. Early termination (study ended early) on 30-Dec-1999.

Source: Response to FDA Request for Information Dated 24-May-2013 (question 3); submission 24 Jun 2013; Table 3-14 (revised)

Patients with Lipodystrophy

There were seven known events of cancer, including three cases of T-cell lymphoma, in the NIH and FHA101 trials. Further details are presented below.

- T-cell cutaneous lymphoma: At study entry, patient 90115 (NIH Trial) was a 68-year-old man with AGL, as well as severe insulin resistance, diabetes mellitus, hypertriglyceridemia, abnormal liver function tests, and hepatosplenomegaly. In July 1997, five years prior to starting metreleptin (May 2002), he was evaluated for leukopenia (WBC 2000/µL) with relative neutropenia and was diagnosed with chronic idiopathic neutropenia. A lymph node biopsy and bone marrow biopsy in 1998 were non-diagnostic. Erythropoeitin was prescribed started in 2001. In early May 2002, another bone marrow biopsy showed a markedly hypercellular marrow with erythroid predominance and reactive lymphoid nodules. Peripheral blood smear showed moderate leukopenia, mild normochromic, normocytic anemia, and mild thrombocytopenia. In mid May 2002, the patient was evaluated at the NIH for generalized lipodystrophy and started on metreleptin treatment, while still taking erythropoietin. At the time of initial evaluation, he was noted to have diffuse lymphadenopathy on exam as well as 1-2 small skin lesions on his leg that did not appear concerning on a background of sun-damaged skin. He received a trial of G-CSF of unspecified duration from his local hematologist for leukopenia. At a four-month follow-up visit at the NIH, a liver biopsy showed no specific features of steatohepatitis, and abdominal ultrasound showed splenomegaly. He continued to have lymphadenopathy on exam. At his eight-month follow-up visit, repeat abdominal ultrasound showed no change in the splenomegaly. Over the preceding month, the patient had noted progression of the skin lesions on his leg with increased size and number of the lesions. Skin biopsy revealed peripheral T-cell

lymphoma. Metreleptin treatment was discontinued at that time. Bone marrow biopsy performed the next month showed hypercellular bone marrow with trilineage hematopoiesis, erythroid hyperplasia, and atypical lymphoid infiltrate suggestive of involvement by peripheral T-cell lymphoma. On peripheral blood, clonal rearrangement of the T-cell receptor gamma chain was detected. Based on the fact that the skin lesions were present at baseline prior to initiation of metreleptin treatment, and given that the progression could be consistent with the natural history of the condition, the peripheral T-cell lymphoma was not reported as an adverse event at that time.

Reviewer comment: The correlation between metreleptin and the development of T-cell lymphoma is confounded by signs of myelosuppression at baseline, the use of another cytokine (G-CSF), and abnormal bone marrow biopsies prior to initiation of metreleptin therapy. In addition, the patient was taking erythropoietin, and had lymphadenopathy, hepatosplenomegaly, and skin lesions before starting metreleptin.

- T-cell lymphoma / breast cancer: At study entry, patient 90147 (NIH Trial) was a 59-year-old female from Spain who was first seen at the NIH in May 2008 for evaluation and treatment of AGL that had developed over the past 10 years. She had a recent history of neutropenia diagnosed in Dec 2007 for which she was briefly treated with G-CSF (Neupogen) with normalization of her neutrophil count. However, the neutropenia recurred in Jan 2008, and the G-CSF was restarted. On 11 Jan 2008, a bone marrow biopsy revealed hypercellular bone marrow with marked atypical T-cell lymphocytosis and myeloid maturation with left shift. At her baseline visit at the NIH in 2 Jun 2008, her WBC was normal at 7240/µL with a normal neutrophil count of 2150/µL, and elevated lymphocyte count of 4200/µL (on G-CSF treatment). She was started on metreleptin on 04 Jun 2008, and returned home to Spain to continue metreleptin treatment. This was her only visit to the NIH. The patient had a history of a benign breast fibroma. In Oct 2008, she was diagnosed with intraductal breast carcinoma. In (b) (6), she underwent a right complete mastectomy. Lymph nodes (43) were clear. She was treated with tamoxifen. On an unspecified date, the patient's husband reported that she experienced sores in her throat, a persistent cough, and after approximately 10 days, developed blurry vision. She was diagnosed with cataracts. The patient then developed skin nodules and corneal ulcers. A skin biopsy performed in Jan 2009 revealed cutaneous T-cell lymphoma, stage IV-A. On an unspecified date in Feb 2009, CD4+ T-cell lymphoma infiltration was seen in cerebrospinal fluid; data suggested an "SP infiltration" (not defined further) through clonal lymphoid T-cells. A CT scan performed on 20 Feb 2009 showed hepatosplenomegaly, with a small cystic lesion in the right hepatic lobe (both similar to previous imaging studies performed on 22 Jan 2009). It did not show significant changes in terms of lymphoma staging. The patient was instructed to stop metreleptin by the investigator after tapering down for one week. The last dose of metreleptin was taken on 31 Jan 2009. Chemotherapy treatment was initiated on

19 Feb 2009 utilizing fludarabin, cyclosphosphamide, and doxorubicin. Tamoxifen was suspended while undergoing chemotherapy treatment. She was discharged on an unspecified date with a hemoglobin of 8.0 g/dL (normal range: 12.0-16.0 g/dL), platelet count of 99.0 x 1000/µL (normal range: 150.0-425.0 x 1000/µL), elevated peripheral leukocyte count of 17.4 x 1000/µL (normal range: 4.0-11.0 x 1000/µL) and peripheral neutrophils 14.5 x 1000/µL (normal range: 1.9-8.0 x 1000/µL). Her peripheral lymphocyte count was normal at 2.2 x 1000/µL (normal range: 0.9-5.2 x 1000/µL). She was scheduled to start her third cycle of chemotherapy on 04 Mar 2009. Based on subsequent information from the investigator, the patient died on (b) (6) (b) (6). According to the patient's husband, the cause of death was "multi system organ failure related to the lymphoma." According to the investigator, "leptin did not cause the lymphoma but may potentiate the paraneoplastic tendencies inherent in the underlying disease of the patient."

Reviewer comment: The correlation between metreleptin and the development of T-cell lymphoma is confounded by signs of myelosuppression at baseline, the use of another cytokine (G-CSF), and abnormal bone marrow biopsies prior to initiation of metreleptin therapy.

- Metastatic papillary thyroid carcinoma: At study entry, patient 90156 (NIH Trial) was a 22-year-old Hispanic female patient with CGL and a relevant past medical history of Hashimoto's thyroiditis of unknown duration. The patient was diagnosed with multiple thyroid nodules in the summer of 2009 (month unknown), approximately a few months after starting metreleptin. In Nov 2010, during a visit to the NIH clinical study site, an ultrasound of the thyroid showed seven nodules (two left, two right, three isthmus). Fine needle aspiration showed some nodules to have atypia of undetermined significance (suspicious of thyroid cancer). On (b) (6), after approximately 1.9 years of treatment with metreleptin, the patient was admitted to the NIH for a total thyroidectomy. Pathology results showed metastatic papillary thyroid carcinoma involving one lymph node, multifocal papillary cancer involving the right isthmus/pyramidal and left lobes, and Hashimoto's chronic thyroiditis. The patient was discharged on (b) (6) without complications. According to documentation provided in the four-month safety update, the patient received definitive treatment with I-131 radioablation on 9 Jan 2012.

- Progressive adenocarcinoma: The narrative for this event was presented in Section 7.3.1, Deaths.

- Anaplastic large cell lymphoma: At study entry, patient 90170 (NIH Trial) was an 11-year-old female with AGL. Relevant medical history included hypertension, hypertriglyceridemia, hyperlipidemia, severe insulin resistance, and non-alcoholic steatohepatitis with possible cirrhosis. Her only medication was metformin 750 mg BID for severe insulin resistance. She had no known autoimmune disease or hematologic abnormalities, and there was no family history of malignancy or

autoimmune diseases. A comprehensive work-up for autoimmune markers (including antinuclear Ab, anti-ENA, thyroid peroxidase Ab, anti-thyroglobulin Ab, GAD65 Ab, anti-cardiolipin Ab, antimitochondrial Ab, anti-neutrophil cytoplasmic Ab, rheumatoid factor) was negative, and complement and quantitative immunoglobulin levels were normal. Baseline labs included HbA1c 5.3%, FPG 108 mg/dL, insulin 251 uIU/mL, TG 368 mg/dL, ALT 36 U/L, AST 20 U/L, WBC 4.51 x 103/µL (50% neutrophils, 34% lymphocytes, 14% monocytes, 2% eosinophils, 1% basophils), hemoglobin 13.2 g/dL, hematocrit 36.8%, platelet 188 x 103/µL. Routine chemistry was normal. Liver biopsy obtained on 07 Oct 2010 showed mild steatosis with minimal inflammation and possible cirrhosis. The patient initiated metreleptin treatment on 22 Feb 2011 based on severe insulin resistance and significant liver disease with possible cirrhosis on liver biopsy. The patient presented to the NIH on 12 Dec 2012 for an unscheduled visit for evaluation of a mass around her right breast (two week history). She was found on exam to have a visible mass just inferolateral to the right lower quadrant of the right breast. The overlying skin showed a very slight purplish color change. The skin could not be lifted off the mass completely but was also not puckered upon elevation of the breast. On palpation, the mass measured about 5 by 4 cm and was minimally tender. It was not fixed but motion was relatively restricted. There was one solitary 1 cm diameter right axillary lymph node noted on palpation, which was shotty, fairly mobile, nontender, and not fixed. The CBC on 12 Dec 2012 showed WBC 10.9 x 103/µL (69% neutrophils, 19% lymphocytes, 6% monocytes, 4% eosinophils, 1% basophils), hemoglobin 11.9 g/dL, hematocrit 35.1%, platelet 460 x 103/µL). A magnetic resonance imaging scan showed an ovoid heterogeneously enhancing mass in the right anterolateral chest that was separate from breast tissue, measuring 3.4 x 3 x 1.5 cm, with right internal mammary lymphadenopathy but no axillary lymphadenopathy. On 13 Dec 2012, two core needle biopsies of the mass were performed. Pathology results available on 20 Dec 2012 showed anaplastic large cell lymphoma (ALCL) that was CD30 positive and stained positive for ALK (anaplastic lymphoma kinase), indicating a T-cell lymphoma. Molecular diagnostics of the core biopsy showed a clonal T-cell population consistent with the diagnosis of ALCL. Fluorescent in-situ hybridization demonstrated the ALK rearrangement present in 89% of cells (normal <10%). The patient returned home after the biopsy with arrangements to return for staging and possible excisional biopsy. Metreleptin therapy was ongoing at discharge. On (b) (6) (b) (6), the patient was admitted to the NIH for further evaluation. The patient and her mother reported that in the intervening ~2 weeks, since the Dec 12 evaluation at the NIH, the mass had decreased in size. Metreleptin was stopped on (b) (6) and fenofibrate 145 mg once daily was started. On examination by the same physicians who examined her on Dec 12, the mass was still palpable but clearly reduced in size, as was the right axillary lymph node. On (b) (6), a positron emission tomography scan showed mild enhancement of the primary lesion (SUVmax 2.31) and only minimal uptake in the right axilla. Examination of CSF on (b) (6) was negative for malignant cells. Bilateral iliac crest bone marrow biopsies performed on (b) (6) showed normocellular marrow with progressive

trilineage hematopoiesis and no evidence of lymphoma. On (b) (6), the patient underwent excisional biopsy of the mass. The pathology report confirmed the diagnosis of anaplastic large cell lymphoma. Immunohistochemical stains showed rare atypical CD30-positive and ALK-positive cells in a similar distribution. Molecular studies did not show a T cell clone similar to that seen in the core biopsy, most likely secondary to the paucity of neoplastic cells. The event of T-cell lymphoma was reported resolved on 14 Dec 2012. The patient continued participation in the study as of the data cutoff date of 11 Jan 2013. Follow-up information available from the site indicated that on 23 Jan 2013, the patient was readmitted to the NIH for follow-up. On physical exam, she had a new, firm, mobile, non-erythematous, slightly tender mass at the site of the excisional biopsy, measuring 4 by 4.5 cm. MRI with gadolinium contrast demonstrated a non-enhancing, homogeneously T2 hyperintense ovoid lesion, compatible with a seroma versus an evolving hematoma at the site of the excisional biopsy. There was no evidence of residual or recurrent disease – specifically, both the primary tumor and the previously noted internal mammary lymph nodes were no longer visualized. Needle aspiration of the cystic mass was performed on 25 Jan 2013 and flow cytometry of the aspirate was suspicious for a T-cell population. A decision was made to re-start metreleptin therapy due to concern regarding dose-limiting hepatic toxicity of potential chemotherapy for the lymphoma, and metreleptin was reinitiated on 12 Feb 2013.

Reviewer comment: In contrast to the other two cases of T-cell lymphoma, this patient did not have a baseline hematologic abnormalities or a history of autoimmune disease, although AGL might be considered an autoimmune disease (all three cases of T-cell lymphoma occurred in patients with AGL). Metreleptin is not genotoxic, so unlikely to have contributed to the development of lymphoma (ALK-positive); however, whether or not metreleptin could have contributed to tumor promotion in this case remains unknown.

7.6.2 Human Reproduction and Pregnancy Data

Hypothalamic hypogonadism is seen in congenital leptin deficiency; treatment with metreleptin in these patients induces pulsatile luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion at the time of puberty. In lipodystrophy, the hyperinsulinemic state associated with severe insulin resistance is associated with hyperandrogenic features in females.

The following table was taken from a publication that described metreleptin treatment in a subset of patients with generalized lipodystrophy from the NIH.[119] In the female patients described in this publication, it was proposed that metreleptin plays a role in normalizing menstrual function.

Table 85. Examples of Menstrual Function in Female Patients with Generalized Lipodystrophy Before and After Receiving Metreleptin

Menstrual function before and after r-metHuLeptin therapy

Patient	Baseline menstrual status	12 mo menstrual status
NIH 1	Menses once a year	Regular menses
NIH 2	Primary amenorrhea	Regular menses
NIH 3	Regular menses	Regular menses
NIH 4	Primary amenorrhea	Regular menses
NIH 5	Primary amenorrhea	Regular menses
NIH 6	Hysterectomy without oopherectomy	Hysterectomy without oopherectomy
NIH 8	Irregular menses	Regular menses
NIH 13	Primary amenorrhea	Regular menses
NIH 19	Irregular menses	Regular menses
NIH 20	Irregular menses	Regular menses

Source: Reference 119

Reviewer comment: These data cannot be verified. Given that Patient 90113 was 12 years old prior to starting metreleptin, the diagnosis of "primary amenorrhea" seems premature.

As of the data cutoff for the four-month safety update, four pregnancies were reported among 90 patients enrolled in the trial: two live births (Patients 90105, 90140), one premature labor and delivery of nonviable fetus (Patient 90156), and one miscarriage (Patient 90152).

Two pregnancies were captured as serious adverse events and discussed in Section 7.3.2, Nonfatal Serious Adverse Events. Patient 90105 delivered an infant who required full resuscitation at birth and had complications of shoulder dystocia and Erb's palsy. Patient 90156 experienced premature rupture of the membranes with subsequent fetal death.

The following are descriptions regarding what is known of the other two pregnancies:

- Patient 90140: At study entry (22 May 2007), this was a 14-year-old Native American female with CGL and relevant medical history of acanthosis nigricans, asthma, hepatomegaly, hepatosteatosis, and diabetes. On an unknown date in July 2012, the patient contacted the site and informed them she was approximately 12 to 13 weeks pregnant. The patient's last menstrual period was not provided. At that time, the patient was in her fifth year of metreleptin treatment and was reportedly doing well with control of her metabolic parameters. In the past, when not on metreleptin, the patient reportedly experienced extreme metabolic abnormalities of hypertriglyceridemia and hyperglycemia with high dose insulin requirements (greater than 500 units per day). The investigator felt it would be difficult to maintain normal

metabolic pattern without metreleptin treatment through the pregnancy and there was concern regarding risk of hyperglycemia with respect to the fetus. It was decided to continue metreleptin therapy. On an unspecified date in (b) (6) the patient delivered a baby girl. No further information was provided.

- Patient 90152: At study entry (14 Jan 2009), this was a 30-year-old white female with FPL and relevant medical history of pre-eclampsia, pancreatitis, fatty liver, nonalcoholic steatohepatitis, hepatomegaly, polycystic ovary syndrome, hyperlipidemia, insulin resistance, diabetes, and hypertriglyceridemia. In an October 2010 visit, metreleptin treatment compliance was reportedly less than 25%, TG was greater than 7000 mg/dL and the patient had been reportedly using Nuva Ring birth control for one year. In November 2010, the patient called the lead associate investigator at the site and told her she believed she was pregnant. The patient was told to see her local medical doctor and check fasting TG. The patient did not contact the site until mid-December 2010, at which time the patient told the site she had miscarried and that she had not visited her physician. Documentation in the patient's file for the August 2011 visit included the following information: 'In the past year, the patient reports that she had her second miscarriage, this is the first miscarriage following the birth of her twin girls, who are now age 3. She reports following the miscarriage she underwent a D&C and tubal ligation'. The patient was subsequently removed from the study for noncompliance. Her last dose of study medication is unknown. No further information is available. (Note that the miscarriage was reported only by the patient; the site was not able to obtain medical records to confirm the pregnancy.)

As of the data cutoff for the four-month safety update, no pregnancies were reported in FHA101 (N = 35).

In the metreleptin for obesity ISS (Amgen), one pregnancy was reported in a patient treated with metreleptin. No further information was available.

Reviewer comment: The adverse events associated with these pregnancies are likely a result of the co-morbidities in the mothers; it is unknown whether metreleptin contributed to adverse fetal outcomes in these cases. I have some concern regarding the potential for fetal exposure to maternal antibodies; in particular the theoretical risk of neutralizing antibodies (see Section 7.4.6, Immunogenicity) and a congenital leptin deficiency-like condition developing in children born to a mother treated with metreleptin.

7.6.3 Pediatrics and Assessment of Effects on Growth

Of the 72 patients in the NIH trial, 39 (54%) were less than 18 years of age. The assessment of safety in this patient population is challenging, given the relatively small number of patients, the lack of a control group, and the difference in age, time of

diagnosis, or type of lipodystrophy between groups that might impact risk of adverse events. Overall, higher incidences of adverse events and serious adverse events were reported in adults versus pediatric patients. Higher incidences (differing by three or more patients) of adverse events were reported in pediatric patients (less than 18 years) for the System Organ Classes *Cardiac Disorders* and *Metabolism and Nutrition Disorders*. Within System Organ Classes, most of the differences in adverse events were distributed across different preferred terms, except for the preferred term of abdominal pain (five pediatric patients versus no adults).

Of the 28 patients in the FHA101 trial, only 3 (11%) were less than 18 years of age. This reflects the fact that the majority of patients in FHA101 had FPL, which typically presents at an older age.

Pubertal Status

Age of menarche in girls has been shown to be inversely related to serum concentrations of leptin,[120] and in boys, rising leptin concentrations may signal the onset of puberty.[121]

As noted in Section 7.6.2, Human Reproduction and Pregnancy Data, congenital leptin-deficiency is associated with hypogonadotropic hypogonadism and abnormal pubertal development[122] in addition to hyperphagia and extreme obesity. Leptin-deficient *ob/ob* mice and humans administered recombinant leptin restored fertility[123] and normal puberty.[124] Recombinant leptin in patients with congenital leptin deficiency induces pulsatile luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion at the time of puberty.[125]

By contrast, patients with lipodystrophy (females) demonstrate the hyperandrogenism associated with insulin resistance, akin to the polycystic ovarian syndrome (PCOS).[119] In the NIH trial, at baseline, six (15%) out of 39 pediatric patients had a history of pubertal disorders, two with precocious puberty and four with delayed puberty. Tanner staging and assessment of pubertal development were not collected on case report forms; these data are kept on file at the NIH. The following table from the NIH investigators list pubertal status of the pediatric patients prior to and after metreleptin treatment.

Table 86. Individual Patient Listing of Pubertal Status, NIH Trial Pediatric Patients (N=39)

Pubertal Status	CGL	AGL	FPL	APL
Puberty complete or near complete prior to Metreleptin	90102, 90104, 90105, 90122, 90125, 90127, 90133, 90140, 90142, 90160			
Puberty likely complete prior to metreleptin (based on growth data)	90111, 90137, 90153, 90154	90145	90149	
Precocious puberty prior to metreleptin	90131	90148		
Delayed puberty prior to metreleptin	90124, 90164	90101 90109		
Delayed/stalled puberty after metreleptin	90143	90101		
Normal pubertal onset and/or progression on Metreleptin	90113, 90124, 90130, 90134, 90159, 90164, 90167	90110, 90128, 90144 [1] 90150, 90170		90141
Prepubertal before and after metreleptin (normal for age)	90165, 90168, 90169		90166	

CGL = congenital generalized lipodystrophy; AGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; APL = acquired partial lipodystrophy.

Note: Numbers represent individual patient numbers for the NIH studies.

Patients 90101, 90124, and 90164 are listed twice due to their status prior to and during metreleptin treatment.

[1] At time of study entry, patient was assessed by investigator to have APL. As her disorder progressed, the patient's loss of body fat was assessed by the investigator to be more consistent with AGL (Note on file).

Source: Clinical Safety Update, Table 48

The majority [34 (87%) out of 39] of pediatric patients in the NIH trial either had completed or nearly completed puberty (or likely completed) prior to metreleptin, were pre-pubertal before and after metreleptin (appropriate for age), or had normal pubertal onset and/or progression on metreleptin treatment.

Two patients (90101 and 90143) were noted to have delayed puberty after starting metreleptin. Patient 90101 (17-year-old female with AGL) had complete lack of breast development before and after metreleptin treatment (and eventually had breast implants) and had very little documentation of pubertal status after starting metreleptin. She was also extremely ill with other conditions (including pancreatitis, steatohepatitis, nephropathy), which may have contributed to poor pubertal development. Similarly, Patient 90143 (13-year-old female with CGL) was mid-pubertal at time of starting metreleptin with apparent lack of progression on metreleptin but had little documentation of pubertal status, and also was extremely ill with other conditions (cirrhosis, hepatopulmonary syndrome), which may have contributed to poor pubertal development.

Two patients (90124 and 90164) had delayed puberty prior to metreleptin, but had normal pubertal progression after starting metreleptin.

Only three pediatric patients were enrolled in FHA101. The following observations were made regarding pubertal development for these patients:

- Patient 648001 (9-year-old female) was pre-pubertal on study entry and had accelerated pubertal development after initiating metreleptin treatment (except for trailing breast development).

Reviewer comment: Premature development of puberty is a theoretical concern of metreleptin treatment in pre-pubertal patients. This is the only case of premature puberty reported.

- Patient 648016 (11-year-old male) was starting to undergo puberty at the time of study entry and had evidence of age-appropriate progression on metreleptin treatment.

- Patient 648022 (16-year-old female) had primary amenorrhea with developed secondary sexual characteristics at study entry and achieved menarche after nine months of metreleptin treatment.

Linear Growth

Given leptin's effects on pubertal development and weight, linear growth was assessed in pediatric patients. Each NIH pediatric patient who had at least one growth point post-baseline was categorized into one of three categories of stature (short, normal, or tall) at baseline and whether growth was complete or near complete prior to receiving metreleptin (N = 18, 46%). The majority of NIH patients had normal or tall stature prior to metreleptin.

The following table from the NIH investigators list growth of the pediatric patients prior to and after metreleptin treatment.

Table 87. Individual Patient Listing of Growth Status, NIH Trial Pediatric Patients (N=39)[††††††††††††]

Growth Status	CGL	AGL	FPL	APL
Short stature prior to metreleptin	90143, 90164	90101 90109		90141
Normal stature prior to metreleptin	90102, 90104, 90124, 90125, 90127, 90128, 90133, 90137, 90140, 90142, 90153, 90154, 90159, 90160, 90165, 90167, 90168	90110 90145 90150 90170	90166	90162
Tall stature prior to metreleptin	90105, 90111, 90113, 90122, 90130, 90131, 90134, 90148, 90149, 90169			90144
Growth complete or near complete prior to metreleptin	90102, 90104, 90105, 90111, 90113, 90122, 90124, 90127, 90128, 90133, 90137, 90140, 90142, 90149, 90153, 90160	90101 90145		
Normal growth on metreleptin	90130, 90143, 90159, 90168, 90169	90109 90170	90166	90144
Growth acceleration on metreleptin	90164, 90167			
Growth deceleration on metreleptin	90131, 90134, 90148, 90154, 90165	90110 90150		90141 90162

CGL = congenital generalized lipodystrophy; AGL = congenital generalized lipodystrophy; FPL = familial partial lipodystrophy; APL = acquired partial lipodystrophy.
Note: Numbers represent individual patient numbers for the NIH studies.
Patient 90125 was not classified for growth status due to the lack of follow-up data. The patient died of pancreatitis 4 months after starting metreleptin treatment.

Source: Summary of Clinical Safety, Table 49

Of 20 patients with growth pattern assessed pattern (normal, accelerated, or decelerated), nine patients had normal growth, two had accelerated growth, and nine patients had growth deceleration on metreleptin. The sponsor notes that growth deceleration likely represents a normalization (or partial normalization) of rapid growth prior to metreleptin, although the sponsor also provided additional reasons for possible growth deceleration:

- Earlier than average puberty leading to earlier growth spurt, and hence, crossing of growth centiles downward

- Improvement in insulin resistance leading to less hyperinsulinemia driving excessive growth

[††††††††††††] There are a number of errors in this table. Patient 90128 has AGL, not CGL. Patient 90144 was apparently re-categorized as having AGL rather than APL. Patient 90148 has AGL, not CGL. Patient 90149 has FPL, not CGL. Patient 90162 has AGL, not APL. I am unable to verify the growth data on this table, given that these data were not captured on case report forms.

- Metreleptin-induced weight loss leading to failure of linear growth, which did not appear to be the case for most patients

Reviewer comment: I am unable to verify whether any or all of the possibilities may be true for any individual patients, as these data were not provided. Note that patient 90141 (10-year-old female with APL) had short stature at baseline and growth deceleration on metreleptin. No further details were provided, but this finding was not reported as an adverse event. No patients with tall stature at baseline had accelerated growth on metreleptin.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the NIH studies, there were four reports of acute pancreatitis (5.6%) with discontinuation of, and/or noncompliance with, metreleptin treatment. All four patients had a prior history of pancreatitis and hypertriglyceridemia. Three of the four reports were deemed serious, and all four were assessed as unrelated to metreleptin.

Reviewer comment: Although some of these case reports did not provide comprehensive documentation of rapid increase in TG in the setting of abrupt discontinuation of metreleptin (as discussed in Section 7.3.5, Submission Specific Primary Safety Concerns), it is plausible that in patients at increased risk for pancreatitis because of severe hypertriglyceridemia who have substantial improvements in hypertriglyceridemia with metreleptin therapy may have an increased risk of acute pancreatitis if metreleptin therapy is interrupted.

7.7 Additional Submissions / Safety Issues

The sponsor was asked to provide data that supported the recent (March 2013) metreleptin approval in Japan for treatment of lipodystrophy; these data were submitted as a safety information amendment to the BLA. Shionogi Inc. licensed development rights to metreleptin for treatment of lipodystrophy in Japan, Taiwan, and South Korea from Amylin and was solely responsible for the Japanese development program.

In Japan, trial KUTR-003-0 was initiated by Kyoto University in patients with lipodystrophy. Information from the US NIH clinical trials (991265/20010769) was used to support its use in this population. KUTR-003-0 was an open-label dose-escalating trial that enrolled 11 patients with lipodystrophy and was ongoing at the time of Japanese NDA submission. Subsequently, another open-label dose-escalating trial (KUTR-003-1) in four patients with lipodystrophy was initiated by Kyoto University for the duration of 20 weeks. This trial was concluded in April 2012. The types of lipodystrophy were not reported.

Patients from both of trials were given the opportunity to continue metreleptin therapy in a new open-label fixed-dose trial, called 'Advanced medical study' (KUTR-003-2) at three institutions, including Kyoto University.

Trial Name: design [Trial No.]	No. of Patients Subjects [a)]	Dose/Administration	Administration Period	Efficacy Evaluation Items
Physician-oriented clinical study [KUTR-003-1]: non-blinded dose escalation	4	Males: 0.01, 0.02, 0.04 mg/kg Females (<18 years) : 0.015, 0.03, 0.06 mg/kg Females (≥18) : 0.02, 0.04, 0.08 mg/kg Administration QD SC	20 weeks	Glucose metabolism: HbA1c, fasting glucose, fasting insulin Lipid metabolism: triglycerides Liver function: ALT, AST
Clinical Research Study [KUTR-003-0]: non-blinded dose escalation	11	Males: 0.01, 0.02, 0.04 mg/kg Females (<18 years): 0.015, 0.03, 0.06 mg/kg Females (≥18): 0.02, 0.04, 0.08 mg/kg Year 1: BID SC After year 1: QD SC	1 year + continuing administration	Glucose metabolism: HbA1c, fasting glucose, fasting insulin Lipid metabolism: triglycerides Liver function: ALT, AST
Advanced Medical Study [KUTR-003-2]: non-blinded fixed dose	12	Males: 0.01, 0.02, 0.04 mg/kg Females (<18 years): 0.015, 0.03, 0.06 mg/kg Females (≥18): 0.02, 0.04, 0.08 mg/kg	Continuing administration	

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-1

Item	Physician-oriented clinical study	Clinical research study	Advanced medical study
Number of subjects	4	11	12
Administration period for safety evaluation	136－142 days	125－3209 days	3－13 months [1] 12－22 months [2]
Sex (percentage of females [%])	3 females (75.0)	8 females (72.7)	8 females (66.7)
Age (year)	14.5 (7.5)	22.2 (8.1)	22.0 (8.3)
Height (cm)	148.78 (20.73)	157.5 (8.8)	154.57 (13.88)
Weight (kg)	37.850 (11.919)	46.5 (12.7)	40.15 (10.84)

[1] Period between the start of the advanced medical study and the data cut-off date (31 December 2011)

[2] Period between the start of the advanced medical study and the data cut-off date (30 September 2011)

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-2

One death and one adverse event leading to discontinuation of metreleptin were briefly described.

- Patient 10 was a 35-year-old female (unknown form of lipodystrophy) with history of hypertension, hypertriglyceridemia, hyperuricemia, hepatic steatosis, diabetes mellitus, diabetic neuropathy, diabetic retinopathy, and pancytopenia. The patient was treated with the following doses of metreleptin: 0.9 mg for 34 days, 1.8 mg for 34 days, and 3.4 mg for 726 days. On day 791 (of 794 days) of treatment, the patient experienced an adverse event of bile duct cancer. She reportedly died of the bile duct cancer, although details were not provided.

- Patient 8 was a 33-year-old female (unknown form of lipodystrophy). A decrease in the patient's white blood cell count from 3000/µL to 1000/µL was noted, leading to discontinuation of metreleptin (in one area of the patient information, it states this occurred 23 days after starting treatment, in another 1.5 months after starting treatment). For the subsequent two months, the patient was hospitalized and followed up, without apparent improvement in white blood cell counts.

Reviewer comment: It is noted that patient 10 had pancytopenia at baseline, and patient 8 developed leukopenia; it is unclear whether this finding is part of the natural history of the lipodystrophy seen in Japan, or if these patients had AGL. As noted in Section 7.6.1, Human Carcinogenicity, hematological findings have been described with patients with lipodystrophy (AGL) and in some cases may be a risk factor for the development of lymphoma.

The sponsor was also asked to provide safety information from worldwide experience with metreleptin from other investigational and compassionate-use programs. A total of 407 patients have been exposed to metreleptin in these programs.

Table 88. Investigator-Initiated Trials and Compassionate-Use Treatment with Metreleptin

Study	Patient Population	Number of Metreleptin-Treated Patients
Investigator-initiated Trials		
Lipodystrophy (LD) **[1]**	LD patients	83 [2]
Other Indications	Rabson-Mendenhall, HIV-associated LD, obesity, NASH, HA, type 1 DM, healthy subjects	255 [3]
Named Patient Program (Compassionate Use)		
LD **[1], [2]**	LD patients	51 [4]
Primary Leptin Deficiency	Congenital leptin deficient patients	18

LD = Lipodystrophy; NASH = non-alcoholic steatohepatitis; HA = hypothalamic amenorrhea; DM = diabetes mellitus.

[1] Ongoing studies or ongoing treatment, except completed IIT with C. Levy-Marchal as principal investigator.
[2] Number of subjects as of January 2013.
[3] Studies completed except for Rabson-Mendenhall.
[4] Does not count LD patients who initiated metreleptin treatment through other studies (e.g. NIH 991265/20010769, IITs).

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-5

Forty-nine patients reported a total of 74 serious adverse events (17 compassionate-use, 57 investigator-initiated trials). No serious adverse events were reported from trials in healthy individuals, or in patients with type 1 diabetes, Rabson-Mendenhall, or hypothalamic amenorrhea.

Table 89. Serious Adverse Events of Special Interest from Compassionate-Use and Investigator-Initiated Trials [1],[2]

SUBSET OF SAEs MEETING CRITERIA OF AE OF SPECIAL INTEREST	Number of Serious Adverse Events [1], [2]			
	LD (Excluding HIV-Related)	HIV-related LD	Obesity	Total
Category Preferred Term				
All Events	**22**	**1**	**2**	**25**
Cancer, Including Hematological Malignancies	**1**	**1**	**1**	**3**
Breast cancer	1	0	0	1
Squamous cell carcinoma of the tongue	0	1	0	1
Thyroid cancer	0	0	1	1
Renal Adverse Events	**2**	**0**	**0**	**2**
Diabetic nephropathy	1	0	0	1
Tubulointerstitial nephritis	1	0	0	1
Pancreatitis	**5**	**0**	**0**	**5**
Pancreatitis	3	0	0	3
Pancreatitis acute	2	0	0	2
Liver-Related Adverse Events	**0**	**0**	**1**	**1**
Hepatic enzyme increased [3]	0	0	1	1
Cardiovascular Adverse Events	**9**	**0**	**0**	**9**
Acute myocardial infarction	1	0	0	1
Cerebrovascular accident	1	0	0	1
Chest pain	1	0	0	1
Heart transplant	1	0	0	1
Hypertension	1	0	0	1
Myocardial infarction	1	0	0	1
Palpitations	1	0	0	1
Pericardial effusion	1	0	0	1
Peripheral artery bypass	1	0	0	1
Hypoglycemia	**5**	**0**	**0**	**5**
Hypoglycemia	2	0	0	2
Hypoglycemia neonatal	1	0	0	1
Hypoglycemic seizure	2	0	0	2

[1] Summary excludes investigator-sponsored trial 991265/20010769 at NIH.
[2] No SAEs of special interest were reported from IITs in healthy subjects, Rabson-Mendenhall patients, hypothalamic amenorrhea patients, type 1 diabetes patients, or non-alcoholic steatohepatitis (NASH) in LD patients.
[3] Blinded study drug (unknown if metreleptin vs. placebo administered).

Source: Response to FDA Request for Information Dated 24-May-2013, Table 3-7

8 Postmarket Experience

No information regarding the postmarketing experience of metreleptin in Japan (approved for a lipodystrophy indication in Mar 2013) was provided in the BLA. To my knowledge, no other country has approved metreleptin for marketing for any condition.

9 Appendices

9.1 Literature Review/References

Literature was referenced throughout the document. See the list of references at the end of the document.

9.2 Labeling Recommendations

Deferred at this time.

9.3 Advisory Committee Meeting

Scheduled for 11 Dec 2013.

9.4 Protocol Summaries

Original Protocol 991265

Objectives

Core Protocol

1. To determine if metreleptin can be safely administered to a group of patients with generalized lipodystrophy

2. To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with generalized lipodystrophy

Studies at NIH

1. To determine if metreleptin treatment will ameliorate lipid deposition in liver and muscle of patients with lipodystrophy

2. To determine if metreleptin treatment will ameliorate hypogonadotropic hypogonadism seen in some patients

Studies at UTSW

1. To determine if insulin sensitivity will improve with metreleptin treatment in patients with lipodystrophy

Entry Criteria

Inclusion Criteria

1. Males and females > 14 years of age

2. Clinically-significant lipodystrophy, identified by the study physician during the physical examination as an absence of fat outside the normal variation and/or identified as a disfiguring factor by the patient

3. Circulating leptin levels < 4.0 ng/mL in females and < 3.0 ng/mL in males on at least 2 occasions obtained from 3 pooled samples

4. Presence of at least one of the following metabolic abnormalities:

    a. Presence of diabetes as defined by the 1997 ADA criteria
        i. Fasting plasma glucose ≥ 126 mg/dL, or
        ii. 2-hour plasma glucose ≥ 200 mg/dL following a 75 gram oral glucose load, or
        iii. Diabetic symptoms with a random plasma glucose ≥ 200 mg/dL

    b. Fasting insulin > 30 µU/mL

    c. Fasting hypertriglyceridemia > 200 mg/dL

Exclusion Criteria

1. Pregnant women, women in their reproductive years who do not use an effective method of birth control, women currently nursing or lactating within 6 weeks of having completed nursing

2. Persons unable to provide informed consent

3. Known liver disease due to causes other than non-alcoholic steatohepatitis

4. Current alcohol or substance abuse

5. Psychiatric disorder impeding competence or compliance

6. Active tuberculosis

7. Use of anorexigenic drugs

8. Other condition, which in the opinion of the clinical investigators would impede completion of the trial

9. Subjects who have a known hypersensitivity to *E. coli*-derived proteins

Study Design and Methods: Core Study

General Design

4-month open-label trial

Screening

1. History and physical examination: Special attention directed to details listed in the exclusion criteria. The degree of acanthosis nigricans, lipoatrophy / lipodystrophy, and hirsutism / virilization will also be recorded.

2. Laboratory parameters: Fasting glucose, fasting leptin, liver function tests, fasting lipids, complete blood count, fasting insulin, and HbA1c.

Study Assessments

1. Baseline laboratory tests: electrolytes, BUN, creatinine, LDH, CPK, AST, ALT, bilirubin, alkaline phosphatase, calcium, magnesium, albumin, protein, thyroid function tests, urinalysis, urine pregnancy test (if applicable), CBC with differential

2. Metabolic tests: oral glucose tolerance test, insulin tolerance test, resting metabolic rate, lipid profile

3. Estimation of body fat: BMI, skin-fold measurements, leptin concentrations

4. Serum and plasma to be stored for hormone and cytokine evaluations

Drug Dosage and Administration

Metreleptin injections will be injected subcutaneously at doses predicted to achieve 50%, 100%, and 200% of normal leptin concentrations based on a “normal body fat” of 30% in females and 20% in males. The dose of metreleptin needed to achieve a normal leptin concentration (100%) for female children (14 to less than 18 years and adult females will be 0.03 mg/kg and 0.04 mg/kg lean body weight, respectively. The dose of metreleptin needed to achieve a normal leptin concentration (100%) for all males will be 0.02 mg/kg lean body weight.

Patients will be started at 50% of this predicted dose and maintained at this dose for one month. The dose will then be increased to 100% of predicted dose for another month. If this is tolerated, then the dose will be increased to 200% of predicted dose. Thereafter, patients will be maintained at this dose until the end of the study period (4 months). If patients do not tolerate a higher dose, they can continue the trial at the dose they tolerated.

The total daily dose will be administered via subcutaneous injections in two equally divided doses (12 hours apart).

Study Sequence

1. Week 1 (Days 1-7):
    a. Admission to research centers
    b. History and physical examination
    c. RMR after 12-hour fast
    d. Fasting baseline blood work
    e. ITT
    f. OGTT
    g. Center-specific testing
    h. Glucose before each meal and at bedtime
    i. 24-hour glucosuria and other 24-hour urine studies
    j. Begin metreleptin injections on Day 7, with 48-hour observation
    k. Education on in-home glucose monitoring and self-injection techniques

2. Weeks 2-3 (Days 7-21):
    a. Previous glucose-lowering therapies (if applicable) will be tapered to prevent hypoglycemia, if necessary

3. Week 4 (Days 22-28):
    a. Return to research centers for repeat of baseline testing
    b. Dose of metreleptin will be increased to 100% of predicted dose in dose is tolerated; patients will be withdrawn if they cannot tolerate 50% predicted dose

4. Weeks 5-8 (Days 29-56):
    a. Patients remain on 100% predicted dose
    b. Glucose monitoring

5. Week 8 (Days 50-56):
    a. Return to research centers for repeat of baseline testing
    b. If patients are tolerating 100% predicted dose, increase to 200% predicted dose

6. Weeks 9-16 (Days 57-112):
    a. At the end of 12 weeks, patients will have blood drawn at their local doctors' offices to check liver function tests and complete blood counts
    b. At the end of 16 weeks, patients will return to the research centers for repeat of baseline testing

Safety Monitoring

Safety will be assessed with physical exam at each visit, weekly symptom sheets and glucose logs, and monthly determinations of liver and kidney function tests, CPK, and complete blood count.

Study Schema

Tests	Baseline	Mo 1	Mo 2	Mo 4
Leptin concentrations	X	X	X	X
Fasting glucose	X	X	X	X
Fasting insulin	X	X	X	X
Fasting lipids	X	X	X	X
Additional chemistry	X	X	X	X
Hematological tests	X	X	X	X
Resting energy expenditure	X	X	X	X
Immunological tests*	X	X	X	X
Bone turnover*	X	X	X	X
Insulin tolerance test	X	X	X	X
OGTT	X	X	X	X
IVGTT*	X			X
TRH/LHRH test*	X			X
CRH test*	X			X
Body fat analysis				
MRI*	X	X	X	X
Anthropometrics	X	X	X	X
Liver fat analysis (MRI)*	X	X	X	X
Pelvic ultrasound*	X			X
Food questionnaire	X	X	X	X
Exercise questionnaire	X			X
Liver biopsy (patients with documented liver abnormalities)*	X			X
Muscle biopsy (optional)*	X			X
Liver and muscle TG and G-6-P at Yale (optional)	X			X
* NIH site-specific studies				

Source: BLA 125390, 15 Dec 2010 submission, Protocol 991265 p35

Secondary Outcome Measures for UTSW

1. Insulin sensitivity
2. Muscle and liver TG content (NMR)

Sample Size

Based on preliminary data in a cross-sectional study, the mean ± SD HbA1c data for eight patients with generalized lipoatrophy was 9.9 ± 2.2%. Assuming a 1.5% decrease in HbA1c over a period of four months, ten patients would be required for 80% power and an alpha of 5%.

Based on this cross-sectional study, the mean ± SD fasting TG data for eight patients with generalized lipoatrophy was 2200 ± 900 mg/dL. Assuming a 660 mg/dL (or 30%) decrease over a period of four months, 12 patients would be required for 80% power and an alpha of 5%.

Therefore, a minimum of 12 patients with both hyperglycemia and hypertriglyceridemia would be needed. Twenty patients between the two centers will be recruited to allow for patients who display only one of the metabolic abnormalities.

Protocol 991265 Amendment 1

The protocol was amended to treat patients for a total of eight months and monitor metabolic control.

Protocol 991265 Amendment 2

After eight months of treatment, patients were offered a withdrawal trial, which would require an inpatient admission and controlled diet. Afterwards, leptin therapy would resume in a long-term extension trial with follow-up visits every six months.

Protocol 20010769 (original)

Objectives

- To determine if metreleptin can be safely administered to a group of patients with lipoatrophy and low leptin levels starting at age 5 and older

- To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with lipoatrophy and leptin deficiency starting at age 5 and older

- To determine if metreleptin treatment will be effective in patients with less severe forms of lipodystrophy (as evidenced by slightly higher circulating leptin concentrations) in terms of improving insulin sensitivity, triglyceride levels, and non-alcoholic steatohepatitis

Entry Criteria

Inclusion Criteria

1. Males and females > 5 years

2. Clinically significant lipodystrophy, identified by the study physician during the physical examination as an absence of fat outside the range of normal variation and/or identified as a disfiguring factor by the patient

3. Circulating leptin levels < 6.0 ng/mL in females and < 3.0 ng/mL in males on at least two occasions obtained from pooled samples

4. Presence of at least one of the following:

    a. Diabetes as defined by the 1997 ADA criteria
        i. Fasting plasma glucose ≥ 125 mg/dL, or
        ii. 2-hour plasma glucose ≥ 200 mg/dL following a 75-gram oral glucose load, or
        iii. Diabetic symptoms with a random plasma glucose ≥ 200 mg/dL

    b. Fasting insulin ≥ 30 µU/mL while not on exogenous insulin therapy

    c. Fasting TG > 300 mg/dL

Exclusion Criteria

1. Pregnant women, women in their reproductive years who do not use an effective method of birth control, women currently nursing or lactating within 6 weeks of having completed nursing

2. Persons unable to provide informed consent

3. Known infectious liver disease

4. Current alcohol or substance abuse

5. Psychiatric disorder impeding competence or compliance

6. Active tuberculosis

7. Use of anorexigenic drugs

8. Other condition, which in the opinion of the clinical investigators would impede completion of the trial

9. Subjects who have a known hypersensitivity to *E. coli*-derived proteins

Study Design and Methods

Baseline and study measures are similar to those outlined in protocol 991265. This protocol was only conducted at the NIH site.

The study schema between 1-4 months was as outlined above.

Study Schema: Months 4-12

Tests	Mo 4	Mo 6	Mo 8	Mo 12
Leptin concentrations	X	X	X	X
Fasting glucose	X	X	X	X
Fasting insulin	X	X	X	X
Fasting lipids	X	X	X	X
Additional chemistry	X	X	X	X
Hematological tests	X	X	X	X
Resting energy expenditure	X	X	X	X
Immunological tests	X	X	X	X
Bone turnover	X	X	X	X
Insulin tolerance test	X	X	X	X
OGTT	X	X	X	X
IVGTT	X		X	X
TRH/LHRH test	X			
CRH test	X			
Body fat analysis				
MRI	X	X	X	X
Anthropometrics	X	X	X	X
Liver fat analysis (MRI)	X	X	X	X
Pelvic ultrasound	X		X	X
Food records	X	X	X	X
Exercise questionnaire	X		X	X
Quality of life assessment	X		X	X
Liver biopsy (patients with documented liver abnormalities)	X			
Muscle biopsy (optional)	X			
Liver and muscle TG and G-6-P at Yale (optional)	X		X	

Source: BLA 125390, 15 Dec 2010 submission, Protocol 991265 p35

Protocol 20010769: Amendments

Amendment 1 (2003)

- Sample size increased from 20 to 40 patients.

- Patients evaluated every four months during the first year of therapy (compared to more frequent intervals in the initial protocol). Treatment duration was extended from 12 months to beyond 12 months. If the patient showed no improvements after one year, the study medication was to be withdrawn. If the patient did show improvement, the patient was to be evaluated every six months during the second year of treatment. Following the second year, extending the treatment period on an annual basis was to be left up to the patient, PI, and Amgen Inc.

Reviewer comment: Note that no patients were withdrawn due to lack of efficacy.

- Following the Month 2 visit, patients were to remain on 200% of the predicted dose until the Month 8 visit (vs. Month 12 visit in the original protocol). If the patient's response was not optimal following the Month 8 visit, the dose could be increased up to 300% replacement.

- The dose of metreleptin was changed from "increases of 0.01 mg/kg/day with each increase tested for a minimum of 3 weeks" to "the dose of metreleptin can be increased after the 8-month follow up".

- The protocol was changed from evaluating leptin therapy in "a similar group of patients" to "in children and adult patients"

- Evaluation of cumulative changes from baseline was changed from "evaluation at 1 year" to "evaluation during the study period".

Amendment A (2006)

- Maximum daily dose of metreleptin increased from 0.12 mg/kg/day to 0.24 mg/kg/day. A new dosing chart was included in the Appendix of the amendment.

- Patients were to switch from "BID dosing" to "BID dosing followed by once daily dosing (same total daily dose) of metreleptin after 1 year of BID therapy". If significant decrease in metabolic control (i.e., increase in HbA1c >1% and/or increase in fasting triglycerides >200 mg/dL) occurred after switching to QD dosing, dosing was to revert back to BID dosing.

- The rights to meterelepti̇n were transferred from Amgen Inc. (Amgen) to Amylin Pharmaceuticals Inc (Amylin).

- Follow up liver biopsies were changed from "8 months after starting leptin therapy" to "at least 12 months after starting leptin therapy".

Amendment B (2007)

- The sample size was increased from 40 to 75 patients.

- Water for reconstitution was changed from "previous sterile water for reconstitution (vials considered single use after reconstitution)" to bacteriostatic water for reconstitution of metreleptin allowing multiple doses to be used from a single vial (up to 3 days)."

- Collection of three morning fasting samples to be pooled for leptin concentrations was changed to collection of just one sample for measurement of leptin.

Amendment C (2008)

- Metreleptin was changed from "BID dosing followed by once daily dosing (same total daily dose) of metreleptin after 1 year of BID therapy" to "Initiate at QD dosing to improve compliance as metabolic effect did not appear to be compromised; patients were to be switched to BID dosing only if dose and patient treatment warranted."

- Sterile water could continue to be used for reconstitution of metreleptin in those patients on daily doses of metreleptin such that ability to use multiple doses from same vial was not relevant.

- Upper limit of baseline leptin level for inclusion criteria was increased from 6 ng/mL to 12 ng/mL for females and from 4 ng/mL to 8 ng/mL for males.

Amendment D (2009)

- Lower limit on age inclusion criteria was lowered from 5 years of age to 6 months of age (only sterile water can be used for reconstitution in patients under 3 years of age)

- Inclusion criteria were altered to allow for postprandial TG > 500 mg/dL in cases where fasting was not clinically indicated (e.g., in infants)

- Exclusion criteria modified to exclude patients with acquired lipodystrophy with hematological abnormalities such as neutropenia or lymphadenopathy

- Note the updated objectives:

    - To determine if metreleptin can be safely administered to a group of patients with lipoatrophy and low leptin levels starting at age six months

- To determine if metreleptin treatment will be effective in lowering plasma glucose and lipid abnormalities in patients with lipoatrophy and leptin deficiency starting at six months

- To determine in metreleptin treatment will be effective in patients with less severe forms of lipodystrophy (as evidenced by slightly higher circulating leptin concentrations) in terms of improving insulin sensitivity, triglyceride levels and non-alcoholic steatohepatitis (as assessed by both liver volume, serum markers of liver inflammation and function, and liver histopathology)

- To determine effective dose ranges of metreleptin for patients with lipodystrophy

- To devise effective anti-diabetic and lipid-lowering regimens concomitantly with leptin for patients with lipodystrophy and leptin deficiency starting at age six months

Treatment Protocol FHA101 (research version: addendum to amendment 3)

Objectives

Primary

- To provide metreleptin under a treatment protocol to patients with lipodystrophy that is associated with diabetes mellitus and/or hypertriglyceridemia

Secondary

- To monitor the safety and tolerability of metreleptin

- To collect information of the efficacy of metreleptin as assessed by its effects on fasting TG, HbA1c, and fasting glucose

Protocol Design

- Open-label and open-ended and will continue until the study is terminated for administrative or safety reasons

- Dosing

    - Patients will self-inject metreleptin subcutaneously according to the dosing regimen outlined below

  - Metreleptin injections may be administered by a parent, guardian, or care-giver to subjects needing assistance, including young children

  - The recommended starting dose of metreleptin is 0.02 mg/kg BID for 1 month, to be increased to a recommended target dose of 0.04 mg/kg BID

  - The recommended target dose can be increased in 0.02 mg/kg increments up to 0.12 mg/kg BID (or 0.24 mg/kg daily) if the primary treating physician judges that the patient's metabolic improvement is suboptimal

  - The target dose of metreleptin may be reduced in 0.02 mg/kg decrements to 0.02 mg/kg BID or even lower to 0.01 mg/kg BID, if a patient experiences side effects such as excess weight loss or injection-site reactions

  - After subjects are on a stable metreleptin dose and desired improvements in metabolic parameters are observed, subjects may transition from a BID to a QD dosing regimen without altering the total daily dose

- The investigators should schedule follow-up visits with their patients according to the schedule of recommended visits, to monitor each patient's condition and collect basic information regarding treatment efficacy, safety, and tolerability. More frequent visits may be scheduled based on the clinical judgment of the investigator.

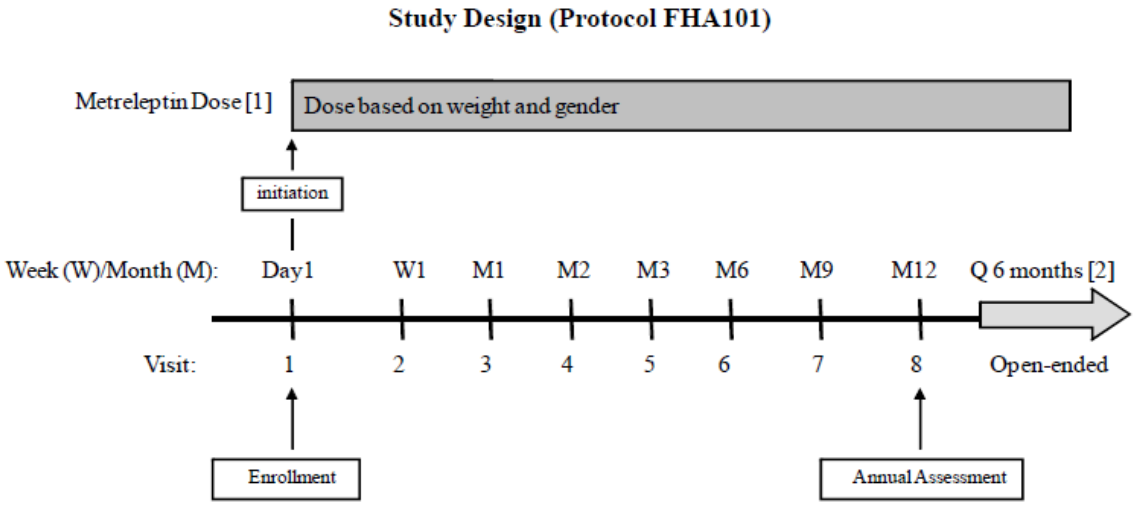
  - Eligible patients will be enrolled into the protocol on Day 1 and will be asked to return to the clinical protocol site in approximately 1 week for Visit 2 (Week 1)

  - Patients should visit their treating physician (the investigator) at least monthly during the first 3 months, and every 3 months thereafter during the first year of treatment

  - Investigators are encouraged to schedule an annual assessment visit approximately 12 months after initiation of metreleptin, at which point the patient and investigator will determine the frequency of subsequent visits as well as the dosing regimen during continued metreleptin treatment

  - Following 1 year of treatment, subject visits should be scheduled every 6 months or more frequently as deemed appropriate by the investigator

Figure 34. FHA101 Study Design



[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.

Source: BLA 125390, Clinical Efficacy Update 27 March 13 Submission, Appendix 2

Study Population

Inclusion Criteria

- Male or female ≥ 5 years old at baseline

- If female of childbearing potential, must:
  - Not be breastfeeding
  - Have a negative pregnancy test result at baseline
  - Practice appropriate birth control

- Has physician-confirmed lipodystrophy as defined by evidence of generalized (whole body) or partial (limbs) loss of body fat outside the range of normal variation

- Has been diagnosed with at least one of the following:
  - Diabetes mellitus
  - Hypertriglyceridemia (TG > 200 mg/dL)

- Has a calculated renal clearance > 40 mL/min; subjects with a calculated renal clearance ≤ 40 mL/min may be included; however, the Medical Monitor should be contacted for dose adjustment

Exclusion Criteria

- Has been diagnosed with HIV infection
- Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being
- Has acquired lipodystrophy and clinically significant hematological abnormalities (such as neutropenia and/or lymphadenopathy)
- Has known infectious liver disease
- Has known allergies to *E. coli*-derived proteins or hypersensitivity to any component of study treatment

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/s/

JULIE K GOLDEN
11/18/2013

ERIC C COLMAN
11/18/2013

CLINICAL FILING MEMORANDUM

BLA Number: 125390 **Applicant: Amylin** **Stamp Date: 12/16/2010**

Drug Name: Metreleptin **BLA Type: Priority**

Background

Lipodystrophy is a group of very rare disorders (approximately 1350 cases reported in the literature[1]), that is characterized by generalized or partial loss of adipose tissue, leading to the inability to store energy in the form of triglyceride (TG) in physiologic adipose tissue sites. Consequently, patients with lipodystrophy develop ectopic deposition of TG in non-adipose tissues such as liver and muscle, leading to insulin resistance, diabetes, hypertriglyceridemia (causing pancreatitis), and steatohepatitis. Because of the loss of adipose tissue, circulating concentrations of the adipocyte-secreted hormone leptin are very low. Leptin, the product of the *ob* gene, plays a central role in the neurohormonal regulation of energy homeostasis and fat and glucose metabolism. The relative leptin deficiency observed in this disease state contributes to hyperphagia, which exacerbates the metabolic abnormalities as patients ingest more fat than they are able to dispose. Current available therapies for lipodystrophy include diet modification and pharmacologic intervention with oral anti-hyperglycemic agents, insulin, and/or lipid-lowering agents.

Metreleptin, a recombinant analog of human leptin, is a 147-amino acid polypeptide that differs from the human leptin sequence by one additional amino acid, methionine, located at the amino-terminal end. Metreleptin is being supplied as a sterile lyophilized cake and is reconstituted with bacteriostatic water for injection (BWFI) with 0.9% benzyl alcohol. It is administered as a subcutaneous injection.

The proposed indication as follows: *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.* The proposed limitations of use include: (1) *Metreleptin is not indicated for use in patients with HIV-related lipodystrophy,* and (2) *Metreleptin is not for use in patients with diabetes mellitus and/or hypertriglyceridemia without concurrent evidence of inherited or acquired lipodystrophy*.

Regulatory History

Note: Bolding indicates key clinical activities in the regulatory history

Date	Activity
29 Mar 1996	**IND 50259 submitted by Amgen**
05 Jun 2000	**IND 60534 submitted by Phillip Gorden from NIH to study metreleptin for lipodystrophy**
16 May 2001	Amgen EOP2 meeting with the Agency (IND 50259) • The Division agreed that study 991265 (8-month initial trial in 9 patients) was sufficient to use as the single pivotal trial in a leptin NDA • The Division suggested that the NDA could be strengthened by following patients during a drug withdrawal and re-treatment period • Concern about off-label use was raised; there was discussion about whether this could be

[1] Garg A. Lipodystrophies: Genetic and Acquired Body Fat Disorders. J Clin Endocrinol Metab. 2011; 96(11):3313-3325.

Date	Activity
	addressed through restricted distribution • The sponsor noted that dose and schedule were developed to achieve replacement levels of leptin, but that TG and glucose levels, rather than leptin levels, were used to titrate the drug • The Division indicated that dosing rationale should be included in the NDA • The Division agreed that sufficient data exist from studies 991265 and 970161 [study in primary leptin deficiency] to support use in pediatric patients • The Division concurred that the safety package consisting of the obesity and diabetes trials conducted with metreleptin would provide sufficient safety data to support the NDA, and that these data could be submitted as an ISS without individual study reports • The Division stated that the indication should identify the disease population and benefits expected with the drug • FDA could not state what the review status (i.e., priority vs. standard) would be at this time • The preclinical program is adequate for the narrow indication/population
22 Aug 2001	**Amgen was granted orphan designation of metreleptin for the treatment of metabolic disorders secondary to lipodystrophy (OD 01-1467)**
06 Sep 2001	Amgen was granted fast track designation of metreleptin for use as hormone replacement in the treatment of congenital leptin deficiency
22 Oct 2001	**Amgen was granted fast track designation of metreleptin for the treatment of metabolic disorders associated with lipodystrophy**
03 Mar 2006	**Amylin assumed sponsorship of metreleptin (IND 50259) from Amgen** Amylin assumed ownership of Amgen's metreleptin inventory manufactured at 2 sites (Thousand Oaks and Lake Centre) and Amgen's master and working cell banks
17 Oct 2007	**Type C meeting convened to confirm Amylin's interpretation of Amgen's EOP2 meeting in 2001 and to obtain DMEP's guidance related to updated clinical and nonclinical data for lipodystrophy** • **Clinical package of 29 patients from NIH trials sufficient** • Non-clinical package sufficient • HIV-related lipodystrophy not within the scope of the proposed indication
01 May 2008	CMC IND amendment filed to add Sandoz GmbH (Kundl, Austria) as an additional manufacturer of drug substance
19 May 2008	**Treatment IND 101824 filed as means to expand access to metreleptin for patients with metabolic disorders associated with lipodystrophy until submission of the NDA** Sandoz GmbH is proposed as an additional drug substance manufacturer for the treatment IND
05 Jun 2008	Teleconference with FDA to discuss using Sandoz drug substance in the treatment IND
08 Jun 2008	FDA authorized the "Treatment IND May Proceed", but only using Amgen drug substance for clinical use FDA indicated that additional work needed to be performed in order to establish comparability between Sandoz and Amgen drug substance, including a 28-day bridging toxicology study
Feb 2009	**FDA was notified about 2 cases of peripheral T cell lymphoma that occurred in the lipodystrophy program (IND 60534)**; in response, Amylin: • Amended the exclusion criteria of the treatment protocol FHA101 (IND 101824) to exclude those patients with acquired lipodystrophy who have clinically significant hematologic abnormalities, such as neutropenia and/or lymphadenopathy • Notified all investigators and physicians who are involved in lipodystrophy clinical trials and compassionate use treatments with metreleptin of these reports of peripheral T-cell

Date	Activity
	lymphoma and assessment of these cases
10 Sep 2009	Amylin provided additional CMC and nonclinical information on metreleptin to qualify Sandoz GmbH as a drug substance manufacturer and to seek agreement that Sandoz drug substance is suitable for clinical use
22 Oct 2009	Request for comments: Amylin proposed filing the lipodystrophy NDA with Amgen drug substance because of its long history of clinical use without apparent safety concerns and continuing stability and based on the large quantity of Amgen drug substance available to supply metreleptin for this small orphan population for the foreseeable future
10 Dec 2009	FDA response indicating lack of concurrence that comparability had been fully established between Amgen and Sandoz metreleptin material by the CMC characterization information provided. FDA recommended against an NDA filing with Amgen drug substance, despite its use to supply the ongoing treatment protocol in lipodystrophy. The lack of a site for pre-approval inspection categorized the Amgen drug substance as out of compliance with Agency policy.
08 Feb 2010	Amgen communicated an intention to file the metreleptin for lipodystrophy NDA with Sandoz material **To expedite availability of this orphan designated drug, Amylin submits "Request for Submission of Portions of an Application" (i.e., rolling review)**
02 Apr 2010	Amylin requested a teleconference with the chemistry reviewer to clarify the scope of the Agency's information requests to facilitate transparency and ensure submission of the appropriate information and data
09 Apr 2010	Agency issued advice/information request for a briefing book and meeting to discuss the development proposal and the following specific issues: • Amylin's plans for sourcing drug substance and drug product • Possible alternative scenarios if drug substance from the proposed new drug manufacturer, Sandoz GmbH, cannot be qualified as comparable to material manufactured by Amgen • The need for additional clinical and nonclinical information if the Sandoz material is not comparable • Amylin's plans for use of Amgen material and Sandoz drug substance within a single NDA • Details on the status and projected timeline for each portion of the lipodystrophy NDA
30 Jul 2010	Agency's acceptance of rolling submission timeline and plans
13 Oct 2010	Letter states that per the Patient Protection and Affordable Care Act the Agency now believed that the appropriate marketing application for metreleptin is a BLA
18 Oct 2010	Agency's acceptance of chemical comparability of the Sandoz material
22 Oct 2010	Amylin submitted a request for Agency's comments regarding Amylin's proposed filing strategy for the CMC portion of the rolling BLA submission, a strategy that would allow compliance with the agreed upon rolling submission achedule
16 Nov 2010	Results of the 1-month toxicology study in mice adequately bridge the Sandoz-sourced metreleptin to the non-clinical data available for the Amgen sourced metreleptin. The non-clinical data support initiation of clinical studies with the Sandoz-sourced metreleptin. **Amylin was asked by FDA to collect anti-leptin antibody data on patients transitioned to as well as those naïve to Sandoz metreleptin and include that information in the BLA safety update.**
15 Dec 2010	**Clinical and non-clinical modules submitted along with draft product label**
03 Feb 2011	Agency requested an assessment of comparability between the Sandoz 2000 L DS and Sandoz 1000 L materials

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Date	Activity
May 2011	**Meeting with Amylin to discuss 2 patients in the obesity program (IND 50259) with neutralizing antibodies to leptin and excessive weight gain**
01 Apr 2012	**Submission of Module 3 including data to establish comparability between Sandoz DS made at 2 different fermentation scales. The submission also included:** • **Clinical Addendum to provide clinical experience with Sandoz DS focusing on Amylin's assessment of the immunogenicity of metreleptin manufactured at Sandoz in comparison with metreleptin manufactured at Amgen** • **Proposed RMP** • **Updated draft labeling**
30 May 2012	**Discuss the completeness of the BLA** **As studies were still ongoing and enrolling subjects, the Agency conveyed that there were additional evaluable data from subjects who had enrolled in these studies after the datacuts of the original Dec 2010 submission and that such data should be included in the BLA at the time of filing**
June 2012	Amylin submitted non-clinical and CMC information amendments to IND 101824, in order to begin dosing patients using metreleptin manufactured at Sandoz at the 1000L scale
11 Jul 2012	**Amylin and Agency had a teleconference to agree on the information/data to complete the BLA** • **Agency specifically requested additional efficacy and safety analyses as well as a comprehensive assessment of immunogenicity (lipodystrophy and obesity)**
22 Jul 2012	**FDA requested additional analyses and specific format for data presentation for Summary of Clinical Safety update, Summary of Clinical Efficacy update, and Clinical Addendum**
Aug 2012	**FDA informed of a 3rd patient in the obesity program (IND 50259) with neutralizing Abs to leptin and excessive weight gain**
23 Oct 2012	Agency recommended Amylin request a pre-BLA meeting prior to submission as outlined under PDUFA V's "The Program"
30 Nov 2012	The Agency received an email from Amylin indicating there may be a possible shortage of metreleptin due to delays in manufacturing of drug product and a shortage of bacteriostatic water for injection (BWFI)
05 Dec 2012	Type A meeting: Discussed the manufacture and clinical use of metreleptin for lipodystrophy Because of possible drug shortage, the company contacted investigators and asked them to stop enrolling any new patients
17 Dec 2012	**Pre-BLA meeting:** • **Agreements confirmed with regard to outstanding clinical documents/data to complete the BLA filing** • Non-clinical information was also confirmed • RMP adequate to mitigate for risks now • A potential exists for a REMS request during review as noted in the preliminary response from FDA • Clarification was received for the 2013 manufacturing campaign
2 Jan 2013	The Agency requested additional information to be submitted with the final section of the BLA in order to facilitate the OSI development of clinical investigator and sponsor/monitor/contract research organization inspection assignments
Jan 2013	**FDA informed of 3rd patient in the lipodystrophy program (IND 60534) diagnosed with lymphoma**
22 Jan 2013	FDA requested lymphoma case analysis and update to Investigator's Brochure and all informed consent forms to include available information about lymphoma in metreleptin-treated patients
29 Jan 2013	FDA provided advice on performing in-process intermediate hold time study
1 Feb 2013	Agency requested a status update on obtaining BWFI for use with metreleptin

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Date	Activity
26 Feb 2013	Amylin submitted a response stating that they do not anticipate any shortage of BWFI as the supply has been secured for the duration of 2013
27 Feb 2013	FDA requested breakdown of clinical data from 11 Jul 2011 cutoff (N = 100) and Jan 2013 cutoff (N = 125) by sex and lipodystrophy subtypes [for oncology consultant] FDA requested estimated date for submission of the last BLA module

Labeling
The sponsor has submitted a draft package insert in PLR format, Medication Guide, and Instructions for Use in Module 1.

REMS
The sponsor has submitted a proposed REMS in Module 1, including Elements to Assure Safe Use (ETASU):

- Prescribers must be certified
  - Prescriber Training Module
  - Prescriber Enrollment Form
  - DHCP Letter
  - Dear Professional Organization Letter
  - MYALEPT REMS Program website

- Pharmacies must be certified
  - Prescription Authorization Form

- Patients must have evidence or other documentation of safe-use conditions

Pediatric Waiver
Not required since orphan designation has been granted.

Site Inspections
The safety and efficacy database for the lipodystrophy population consists of the following:

Study	Patient Population	Number of Metreleptin-Treated Patients	Position in BLA	Endpoints Supported
NIH Studies 991265/20010769 [1]	LD patients	72 [2]	Pivotal	Safety and efficacy
Treatment IND FHA101 [1]	LD patients	28 [3]	Supporting	Safety and efficacy
Amgen 5-study ISS (metreleptin monotherapy)	Obese subjects without LD	784	Supporting	Safety (including immunogenicity)
Other 10 Amgen Obesity Studies (metreleptin monotherapy)	Obese subjects without LD	379 [4]	Supporting	Immunogenicity
Amylin Obesity Program (metreleptin-pramlintide combination)	Obese subjects without LD	615	Supporting	Immunogenicity
Other Investigator-initiated Studies [1]	LD patients Rabson-Mendenhall	92 [5]	N/A	N/A
Compassionate Use Treatment [1]	LD patients	51 [5][6]	N/A	N/A
Compassionate Use Treatment [1]	Congenital leptin deficient patients	18 [5]	N/A	N/A
Other Investigator-initiated Studies in Other Indications	HIV-associated LD, obesity, NASH, HA, type 1 DM, healthy subjects	248	N/A	N/A

LD = lipodystrophy; NASH = non-alcoholic steatohepatitis; HA = hypothalamic amenorrhea; DM = diabetes mellitus.
[1] Ongoing studies or ongoing treatment, except investigator-initiated study with C. Levy-Marchal as principal investigator.
[2] As of 11 July 2011 data cut.
[3] As of 07 Mar 2012 data cut.
[4] Excludes 4 patients with congenital leptin deficiency treated with metreleptin in Amgen Study 970161.
[5] As of January 2013.
[6] Excludes patients who initiated metreleptin treatment through other studies (e.g. NIH studies, other investigator-initiated studies).

I recommend inspecting:

Site	Name, Address, Phone Number, Email, Fax #	Protocol ID	# Subjects Enrolled	Indication
901	Phillip Gorden, M.D. Clinical Endocrinology Branch, NIDDK NIH Clinical Center Building 10, CRC 6-5940 Bethesda, MD 20892 USA Tel: 301-402-7340 Fax: 301-435-5873 Email: gordenp@extra niddk.nih.gov	Completed Study 991265 and ongoing Study 20010769, integrated into a single analysis	72[1]	Lipodystrophy
648	Elif Arioglu Oral, M.D. University of Michigan Department of Internal Medicine Division of Endocrinology and Metabolism 24 Frank Lloyd Wright Dr. Lobby	FHA101	25[2]	Lipodystrophy

	G1500 Ann Arbor, MI 48106 Tel: 734-647-4940 Fax: 734-647-2145 Email: eliforal@umich.edu			
1 As of 11 Jul 2011 data cut 2 As of 07 Mar 2012 data cut				

Filing Checklist

On initial overview of the BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			In the original submission (2010), the Module 2 SCE and SCS were the integrated summaries for lipodystrophy; in the 2013 submission the updates to these summaries are in Module 5. This is acceptable.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			In the 2010 submission, the ISS was the safety summary of the 5 Amgen obesity trials. The 2013 submission also includes in Module 5 a clinical addendum (immunogenicity) and clinical update (see above). This is

	Content Parameter	Yes	No	NA	Comment
					acceptable.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			In the 2010 submission, the ISE references the SCE (Module 2). This is acceptable.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5.6; 2013 submission
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	BLA
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Information limited because of the rarity of the disease; no PK studies done in lipodystrophy; dosing recs empiric; based on OL pivotal trials' efficacy and PD
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			One pivotal trial (combination of ST and LT; NIH 991265-20010769) and one supportive trial (FHA101). This is acceptable.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Orphan indication; studies are small and OL. This is acceptable.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Treatment of metabolic abnormalities associated with generalized and partial familial lipodystrophies (FDA meeting minutes 19 Nov 2007)
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	All studies in lipodystrophy patients to support this BLA (NIH Studies 991265/20010769 and Study FHA101) were conducted in the US.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess	X			Waiver request for

	Content Parameter	Yes	No	NA	Comment
	the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?				TQT evaluation consulted to IRT.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		At least one trial in patients with lipodystrophy was conducted at Kyoto University in Japan, which served as the basis for recent (3/13) Japan approval. (According to Shionogi press release, the NDA was filed 7/12.) Will request information. No worldwide assessment given. Metreleptin is used on a compassionate basis in other countries for primary leptin deficiency and lipodystrophy, but no safety information regarding these programs was provided.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?			X	Orphan indication (chronic). Exposure is adequate.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	First in class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			SAEs, DAEs, deaths, pregnancies 5.3.5.1 NIH CSR 2010, app. 3.24.7 5.3.5.1 FHA CSR

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
					2010, app. 3.7.3 5.3.5.3.3 2013 safety update, app. 6-9 5.3.5.4 pram-leptin CSRs 2013 DFA101 app. 3.10.9 DFA102 app. 3.10.10 DFA102E app. 3.9.6 DFA104 app. 3.11.4 <u>SAEs, deaths only</u> Amgen studies 5.3.5.1 obesity CSRs 2010 5.3.5.4 other leptin trial CSRs 2013
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Clinical data after Amgen to Sandoz DP switch requested.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Metreleptin has been granted orphan drug status; PREA does not apply to any drug for an indication for which orphan designation has been granted under section 526.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and		X		No case report forms were provided for any

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts)?				of the obesity studies.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __x__Yes___No

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The sponsor addressed the clinical requests from FDA reviewers in a teleconference 11 Jul 2012 and at the pre-BLA meeting 17 Dec 2012; therefore, in my opinion, the application is fileable from a clinical perspective.

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

1. **From the metreleptin + pramlintide clinical program provide a safety summary that includes an assessment of:**

- **Deaths, serious adverse events, and adverse dropouts**
- **Adverse events of special interest**
  - **Cancer, including hematological malignancies**
  - **Renal adverse events**
  - **Pancreatitis adverse events**
  - **Liver-related adverse events**
  - **Cardiovascular adverse events, as well as a blood pressure and heart rate assessment**
  - **Hypoglycemia**

2. **Provide Case Report Forms for deaths, serious adverse events, and adverse dropouts from the obesity trials (Amgen and Amylin)**

3. **Provide a safety assessment based on all current worldwide knowledge regarding this product, including:**

- **Recent Japanese approval[4]**
- **Compassionate use for primary leptin deficiency and lipodystrophy**
- **Investigational use**
- **Literature review, including a review of leptin and cancer in humans**

[4] http://www.shionogi.co.jp/ir_en/news/detail/e_130325.pdf

CLINICAL FILING MEMORANDUM

Reviewing Medical Officer	Date
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE K GOLDEN
05/02/2013

ERIC C COLMAN
05/02/2013